VOLUME 50 NOVEMBER, 1943 NUMBER 5

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THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

VOL. 50 NOVEMBER, 1943 No. 5

THE SIMILARITY OF CLINICAL AND ROENTGEN FINDINGS IN CHILDREN WITH EWING'S SARCOMA (ENDOTHELIAL MYELOMA) AND SYMPATHETIC NEUROBLASTOMA*

By ROBERT PHELPS BARDEN, M.D., D.Sc. (Med.)

PHILADELPHIA, PENNSYLVANIA

IN THE recent literature analyzing Ewing's sarcoma and sympathetic neuroblastoma, several observers have noted the marked histopathological similarity between these two diseases, and a few writers have declared them to be identical in pathology.[2,5,6,7,8] It is evident that among these unusual tumors there are borderline states difficult to distinguish one from another by microscopic study.

The typical roentgen appearance of the bone lesions in Ewing's sarcoma and in sympathetic neuroblastoma is well known.[1,2,4,5] However, it is not sufficiently appreciated that the roentgen picture of these two diseases can be identical, and this fact is made more interesting because of the parallel similarity in the histopathology mentioned above.

Recently an opportunity was afforded of studying 4 children, 2 of whom died of Ewing's sarcoma, and 2 of sympathetic neuroblastoma. A comparison of these case histories will show how confusing the differential diagnosis of the two conditions may be from a clinical and roentgenological standpoint. In each case, the histopathologic diagnosis was confirmed by several pathologists, subject to the limitations noted in the literature.[2,6,7,8]

CASE 1. C. D. This five year old white boy was first admitted to the Episcopal Hospital in February, 1940, with a history of pain in the joints and recurrent fever for seven months. During this time he had been treated for acute rheumatic fever, without improvement.

Physical examination on admission showed a pale, undernourished boy with swollen tender knees, and tenderness along the shafts of the bones in each leg. The spleen was not palpable. The initial blood count showed a marked secondary anemia and a white blood count of 2,000 with 68 per cent lymphocytes. Occasional immature cells were seen in the blood smear.

Roentgenograms of the skeleton showed numerous punched-out areas of rarefaction in the skull, pelvis, and near the diaphyses of the femora and tibiae. All the long bones showed a striking, smooth, regular, periosteal proliferation extending along the shafts. The provisional clinical and roentgen diagnosis was aleukemic lymphatic leukemia.

During the next two months enlargement of the liver, spleen and lymph nodes appeared. A

* From the Department of Radiology, Hospital of the Protestant Episcopal Church, Philadelphia, Pennsylvania.

FIG. 1*a*. Case 1. Roentgenogram of skull of child with widely distributed Ewing's sarcoma, showing a diffuse fine mottling without the discrete areas of bone destruction so often seen in this condition.

sternal puncture was done in May, 1940, and several pathologists agreed that the smear showed the picture of Ewing's sarcoma.

General body irradiation caused temporary improvement, but by October, 1940, the patient was failing rapidly. The white blood count never rose above 2,000 with a persistent neutropenia and in the terminal stage of the illness the total count fell to 500 with polymorphonuclear forms absent.

The essential findings at necropsy were replacement of bone marrow by fat and grayish tumor tissue, and a few small tumor nodules in the liver. The lungs and adrenals were not involved by tumor. Histopathologic study showed marked endothelial hyperplasia of lymph nodes with evidence of new blood cell formation and invasion and replacement of bone marrow by Ewing's sarcoma.

Comment. This patient first presented the picture of aleukemic lymphatic leukemia with roentgen evidence of widespread destruction of bone. The subsequent findings indicated that the leukemoid blood picture was due to the overwhelming invasion of bone marrow by tumor other than leukemia. Because of the extent of the bone involvement and the subperiosteal and diaphyseal location of the changes seen on the roentgenograms, the revised clinical diagnosis was neuroblastoma, in spite of the histopathologic diagnosis obtained by bone marrow aspiration. Final examination showed no possible primary neuroblastoma, and confirmed the biopsy report of Ewing's sarcoma.

CASE II.* J. J. This two year old white female was admitted to the Children's Hospital in December, 1937, because of increasing pallor, weight loss and pains in the legs of three months' duration. The past history was irrelevant.

Physical examination on admission showed a pale, chronically ill child with ecchymoses over the right eye, shoulder and thighs. The liver was palpable but the spleen was not. There was a marked secondary anemia. Bone marrow smears showed hyperplasia of all elements. Roentgenograms of the bones showed many areas of rarefaction throughout the skeleton with rather uniform periosteal proliferation along the shafts of both femora and tibiae. Intravenous urogram showed normal urinary tracts. Roentgenogram of the lungs was normal.

During the four months before the patient's death there were irregular bouts of fever often associated with increased bone pain. Transfusions caused only temporary improvement. Hard tumor masses developed over the right mandible, the forehead and above each knee.

At necropsy the significant gross findings

* Courtesy of Dr. Ralph S. Bromer and Dr. Rolfe M. Harvey, Department of Radiology, Children's Hospital, Philadelphia.

FIG. 2*a*. Case II. Roentgenogram of child with sympathetic neuroblastoma of left adrenal. The primary tumor was very small. Note the even mottling near the vertex of the skull, with widening of the coronal suture due to increased intracranial pressure.

FIG. 1*b*. Case I. Roentgenograms of child with widely distributed Ewing's sarcoma. The long bones of the legs contain ragged areas of bone destruction especially at the diaphyseal ends. The periosteum is shown as a fine pencil line encasing the shafts, as a result of elevation by tumor immediately beneath it. Compare with Figure 2*b*.

FIG. 2*b*. Case II. Roentgenograms of child with sympathetic neuroblastoma of the left adrenal. The bones of the legs show moth-eaten areas of destruction most marked near the diaphyses. In addition there is marked periosteal proliferation as a result of a layer of metastatic tumor immediately beneath the periosteum. Compare with Figure 1*b*.

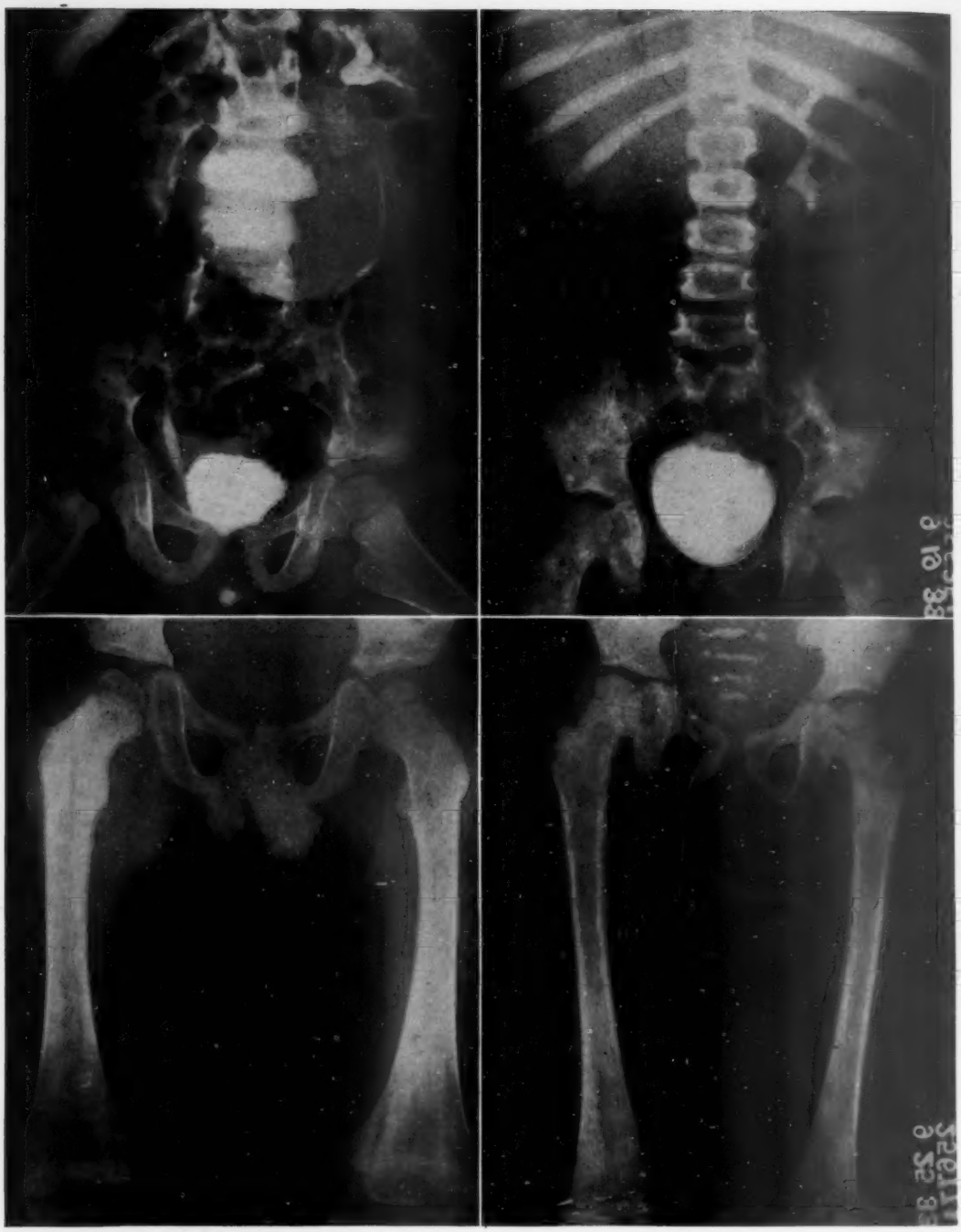

FIG. 3. Case III. Roentgenograms of child with Ewing's sarcoma. Note the large soft tissue mass in the left mid-abdomen displacing the kidney upward and the ureter to the left. The adjacent third lumbar vertebra shows irregular enlargement and marked increase in density. The fourth lumbar vertebra is also invaded by tumor. Note the increased density and elevation of the periosteum in the upper third of the right femur due to tumor involvement. Compare with Figure 4.

FIG. 4. Case IV. Roentgenograms of child with sympathetic neuroblastoma. Note the large soft tissue mass in the right upper abdomen with downward displacement of the pelvis of the right kidney. Along the shaft of each femur the periosteum is elevated and some new bone proliferation is taking place, as a result of tumor metastases in the subperiosteal structures. Compare with Figure 3.

were tumor nodules involving the lungs, liver, peritoneum, paravertebral lymph nodes, and skeleton. There was a small, rounded tumor arising from the superior border of the left adrenal.

Histopathological examination revealed the tumor to be composed of masses of small cells with small, rounded nuclei. There were a few larger cells with vesicular nuclei resembling the ganglion cells of nervous tissue. The pathological diagnosis was adrenal neuroblastoma.

Comment. No abdominal tumors were discovered in this patient before death. The extensive involvement of the skeleton by tumor simulated almost exactly the findings in Case I. Orbital metastases are described as a fairly regular consequence of adrenal sympathetic neuroblastoma, but as will be seen in Case III which follows, similar metastases occur in Ewing's sarcoma. This case, then, although conforming closely to the description of sympathetic neuroblastoma in the literature, combined features of Cases I and III, both of whom had Ewing's sarcoma.

Case III.* S. R. This two year old white boy was admitted to Temple University Hospital in October, 1940, complaining of severe pains in the lower back and legs of seven months' duration. For four months there had been paralysis of the lower extremities, bladder and rectum. He had lost 13 pounds in weight.

The essential physical findings on admission were evidence of healed rickets and a mass in the middle and left upper abdomen, as well as complete transverse myelitis in the lumbar cord.

Roentgen examination showed increased density of the third and fourth lumbar vertebrae and a mass in the abdomen displacing the left kidney upward and laterally, but distinct from it. The provisional clinical and roentgen diagnosis was neuroblastoma.

A needle biopsy of the abdominal mass was performed and the histopathologic diagnosis was "malignant tumor, probably of mesothelial origin." The possibility of Wilms' tumor was mentioned.

Roentgen irradiation, using small daily doses, over the abdominal mass produced diminution in its size and return of some motor function in the lower extremities. Improvement was fleeting, however, and within a month the patient had failed considerably. He developed a large mass in the left orbit with exophthalmos, and destructive lesions in the right femur, ribs and bones of the face. Death occurred in February, 1941, five months after admission and twelve months after onset of symptoms.

Postmortem examination revealed a large retroperitoneal mass in the lumbar region with destruction of the adjacent vertebrae. Smaller retropleural masses lay near the seventh and eighth thoracic vertebrae. Tumor masses were found in many of the bones of the skull. The kidneys and adrenals were normal and no metastases were found in any of the viscera. The histopathologic diagnosis was reticulum-cell sarcoma or Ewing's sarcoma, with the preponderance of opinion favoring Ewing's sarcoma.

Comment. This patient presented findings of a left retroperitoneal mass with displacement of the kidney, invasion of adjacent vertebrae and metastases, particularly to the skull and left orbit. The clinical and roentgenological evidence for sympathetic neuroblastoma was classic. With full knowledge of this, several pathologists agreed on the diagnosis of Ewing's sarcoma.

Case IV.† D. M. This four year old white girl was admitted to the Children's Hospital in September, 1933, with a history of vomiting spells and severe pain in both hips and both arms of four months' duration.

Physical examination on admission showed a large mass in the right upper quadrant of the abdomen. Marked secondary anemia was present and failed to improve with blood transfusions. No abnormality in the white blood cells was found.

Roentgen examination showed downward displacement of the right kidney by the abdominal mass and evidence of bone destruction in the skull, pelvis and both femora. Periosteal new bone was present along the shafts of both femora.

Exploratory laparotomy disclosed a large tumor mass in the right retroperitoneal region, adherent to the vertebral column.

* Courtesy of Dr. W. Edward Chamberlain and Dr. John V. Blady, Department of Radiology, Temple University Hospital, Philadelphia.

† Courtesy of Dr. Ralph S. Bromer and Dr. Rolfe M. Harvey, Children's Hospital, Philadelphia.

Roentgen therapy was ineffective and the patient died in December, 1933, seven months after onset of symptoms.

The pathological report of the tissue removed at operation was sympathetic neuroblastoma.

Comment. This case was so similar to Case III in clinical course and roentgenological findings that differentiation on these grounds is impossible.

DISCUSSION

It is not the purpose of this paper to add confusion to a subject already so controversial as the pathogenesis of Ewing's sarcoma and sympathetic neuroblastoma. It may be that these two diseases are so closely related that they should be considered one complex with varying manifestations. The more likely assumption is that both are distinct tumors composed of cells with the same biological attributes. This would account for the similarity in the elective sites of metastasis. The sequence of events following the implantation of metastases is largely a function of the tissue invaded, according to Willis.[8] Thus the peculiar periosteal proliferation seen in the long bones in each of these conditions results from the presence of tumor immediately beneath the normal periosteal membrane. This reaction of the periosteum is not specific and occurs after any insult located immediately beneath it as, for example, following hemorrhage in scurvy.

From a consideration of the facts brought out in these case histories, however, it is apparent that the conception of Ewing's sarcoma and sympathetic neuroblastoma as distinct clinical, roentgenological and pathological entities should be modified. Widening of the diagnostic concept of these diseases has important practical applications as regards the therapy of Ewing's sarcoma. One of these is that amputation for cure should probably not be attempted in cases diagnosed upon the best evidence as Ewing's sarcoma. This statement is made in spite of the knowledge that a few patients are alive and well five years after the removal of a solitary bone tumor diagnosed as Ewing's sarcoma. Ewing, himself, mentions one of these who died, from irrelevant disease, nine years after amputation.[2] This patient at postmortem showed retroperitoneal nodes containing tumor similar to the original bone tumor.

Another point in therapy is that roentgen irradiation to the retroperitoneal structures is indicated in cases diagnosed as Ewing's sarcoma of bone. The similarity of the case histories in this study emphasizes this need. It would seem wiser to treat all these patients as if the bone tumor were secondary to a hidden abdominal tumor, since it is so often impossible to determine before the postmortem examination which patients actually do have primary abdominal tumors.

In passing, it might be pointed out that Case I illustrates an important fact in clinical pathology which is sometimes forgotten, namely, that a leukemic blood picture does not mean that the patient has leukemia. The possibility of a secondary leukemoid reaction to metastatic invasion of the bone marrow should be kept in mind especially in children showing accompanying roentgen evidence of bone destruction.

CONCLUSION

The case histories of four children with roentgen evidence of widespread bone tumors have been given. While two of these patients died of Ewing's sarcoma and two of sympathetic neuroblastoma, the clinical and roentgenological findings in all were so similar as to make a differential diagnosis impossible before death. This fact is of interest because microscopic differentiation between these two tumors is frequently difficult.

Of more importance is the inference that cases of solitary bone tumors diagnosed as Ewing's sarcoma should be treated as if the bone tumor were secondary to an abdominal tumor whether the presence of the latter can be established or not. This means that amputation for cure should probably

not be attempted; and that roentgen irradiation to the retroperitoneal structures should be routine.*

I wish to thank Dr. William P. Belk, Director of the Pathological Laboratory of the Episcopal Hospital, for his kindness in reviewing the pathological sections on two of the occasions reported above.

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* Since this paper was written a girl, aged two and a half, with lymphatic leukemia was admitted to the University of Pennsylvania Hospital and followed to postmortem examination. Roentgenograms of the skeleton showed changes identical with those in the 4 cases described above.

RENAL DWARFISM OR RENAL RICKETS*

By ROBERT C. MOEHLIG, M.D.
DETROIT, MICHIGAN

THE rapid development of endocrine chemistry with the discovery of potent hormones as well as the rarity of the disease, renal dwarfism, prompts the reporting of a case in which testosterone proprionate was used. Furthermore a somewhat different view than that given by other authors is suggested as the etiology of the disease.

CASE REPORT

R. B., a boy aged five and one-half, was first seen July 8, 1940, with the complaint given by the parents that he was not growing, was undersized, drank large quantities of fluids and passed large amounts of urine at frequent intervals. At the age of one year it was noticed that the infant was smaller than normal. His birth weight was 8 pounds; the delivery was normal. The teeth came in slowly and were smaller than normal. First incisor tooth erupted at the age of ten months. He did not creep until he was eighteen months old and walked at the age of two. He began talking at the age of one year. Enuresis has been present since birth.

It was noted at the age of ten months that he drank large quantities of water and he would awake five and six times at night asking for water. The mother offered him milk but this was refused and his only desire at night was for large quantities of water. He had a craving for lemons. The small size of the child at one year induced the parents to seek medical advice and a physician prescribed thyroid substance grains one-half (.0324) per day. This was continued for six months. At the age of two, 2 cc. of an anterior pituitary growth hormone in the form of "antuitrin T" was given three times a week for twenty doses. No change in growth was noted by the parents. The diabetes insipidus was uninfluenced. A year later he was given a total of 40 cc. of pituitary growth hormone over a period of seven weeks. This was given by the mother, a graduate nurse. At the age of four he complained frequently of headaches.

Past History. The mother was certain that he had not had any of the usual childhood diseases.

Family History. The mother, aged thirty-four, was 58.5 inches (148.5 cm.) in height and weighed 120 pounds (54.4 kg.). She was one of 12 children, having 6 brothers and 5 sisters.

The ages, heights and weights of these were as follows:

Brothers
(Uncles of patient)

	Age	Height		Weight	
		Inches	Cm.	Pounds	Kilograms
A	19	63	160.0	120	54.5
B	22	62	157.5	125	56.7
C	25	63	160.0	125	56.7
D	28	68	172.7	160	72.6
E	37	65	165.0	130	59.0
F	40	64	162.5	160	72.6

Sisters
(Aunts of patient)

	Age	Height		Weight	
		Inches	Cm.	Pounds	Kilograms
A	16	58	147.0	108	49.0
B	24	62	157.5	120	54.4
C	24	62	157.5	120	54.4
D	31	61	155.0	115	52.0
E	36	61	155.0	107	48.5

The youngest of the aunts, aged sixteen, had convulsions during infancy and had "chalky" teeth. She took thyroid substance for several years.

The father, aged thirty-six, was 70.5 inches in height (179 cm.) and weighed 200 pounds (90.7 kg.). He suffered from convulsions and malnutrition in childhood. Before marriage his weight was 120 pounds (54.4 kg.).

There were two other children in addition to the patient, a brother aged two and a sister aged eight; both were apparently normal.

The first born, a boy, died of pyloric stenosis soon after birth.

The patient was an intelligent, bright boy obviously much smaller than a normal boy of five and one-half years (Fig. 1 and 2). His hair was blond and the eyes were blue. Ophthalmoscopic examination revealed bilateral papilledema. His head appeared large and out of proportion to the body.

* From the Department of Medicine, Harper Hospital and Wayne University, Detroit, Michigan.

The measurements were as follows:

	Patient		Normal	
	Inches	Cm.	Inches	Cm.
Circumference of head	19.0	48.0	20.5	52.0
Chest	18.5	47.0	22.0	55.8
Waist	18.0	45.7	20.5	52.0
Span	34.0	86.3	41.6	105.4
Upper	20.0	50.8	23.3	58.4
Lower	13.5	34.0	19.4	49.0
Height	33.5	85.0	43.0	109.0
Weight	23 lb.	10.4 kg.	40 lb.	18.1 kg.

The span was $7\frac{1}{2}$ inches (19 cm.) less than normal, and the height 9 inches (22.8 cm.) less than normal. His weight was $13\frac{1}{2}$ pounds (6.2 kg.) less than normal. The difference between the upper and lower measurements was $6\frac{1}{2}$ inches (16.5 cm.) whereas the normal is 4 inches (10.6 cm.).

Fig. 1. Note short stature, tendency to genu valgum.

The teeth were small (Fig. 3) and poorly developed.

Fig. 2. Lateral view showing hydrocephalic type of skull, pot belly and pes planus.

Fig. 3. Small underdeveloped teeth.

Fig. 4. A very faint outline of the left kidney is shown following injection of diodrast.

The thyroid gland was palpable. The heart was enlarged to the left but the sounds were normal. The abdomen was protruding due apparently to lack of abdominal muscular tone. In the natal fold of the sacrococcygeal region was a pilonidal cyst. The testicles were in the scrotum, but at times would recede into the inguinal canal on exposure to cold. The penis was small. The reflexes were normal. Pes planus was present. There was a mild degree of genu valgum.

The blood pressure was systolic 68, diastolic 30.

The hemoglobin was 75 per cent; erythrocytes 4,340,000; leukocytes 9,650; differential count 62 per cent polymorphonuclear neutrophiles; 34 per cent small lymphocytes; 2 per cent large lymphocytes, and 2 per cent eosinophiles.

The urine was alkaline, the specific gravity ranged from 1.002 to 1.006, and gave a 3 and 4 plus reaction for albumin.

The sediment contained 10 to 15 erythrocytes per low power field.

Phenolsulfonephthalein test gave an output of but 23 per cent in two hours.

The intake and output record for one week as noted by the mother was as follows:

	Intake Ounces	Output Ounces
July 17, 1940	114	99
July 18, 1940	101	98
July 19, 1940	89	81
July 20, 1940	114	99
July 21, 1940	137	120
July 22, 1940	132	125
July 23, 1940	156	140
July 24, 1940	148	139

While in the office he drank 24 ounces of water within a period of twenty minutes.

The blood studies per 100 cc. of blood were as follows:

Calcium	10.8 mg.
	10.4 mg.
	10.6 mg.
Phosphorus	3.1 mg.
Phosphatase	13.5 mg.
Non-protein nitrogen	36.6 mg.
Fasting sugar	0.08 mg.
Blood Kahn reaction	Negative

The roentgen examination of the kidneys was reported as follows:

"Diodrast was given intravenously and the best outlines are demonstrated on the second film exposed following the injection of the dye which was ten minutes following the completion of the injection. The dye has made its appearance in the pelvis and calices of the left kidney but we are unable to make out any dye shadow in the right kidney; there is incomplete

Fig. 5. Hydrocephalic skull outline with flattening and elongation of the sella turcica.

outlining of the kidney pelvis and calices; there is a very low concentration of the dye as shown by the faint shadow of the bladder one and a half hours following the completion of the injection (Fig. 4).

"The roentgenograms of the skull reveal it to be hydrocephalic in type and there is evidence of increased intracranial pressure as shown by the increased digital markings in the inner table of the skull; the sella turcica is flattened and elongated in its anteroposterior diameter as a result of the pressure. No suprasellar cyst or calcification in this area (Fig. 5).

"The roentgenograms of the chest show the heart to be bulbous in type. No thymic enlargement.

"The study of the extremities reveals retarded development as shown by the calcificarion of the carpal bones which correspond to that of a one year old child instead of five years. There are extensive changes about the diaphyseal ends of all the long bones such as is seen in renal rickets." (Fig. 6 and 7.)

On July 13 the patient was placed on thyroid substance gr. ¼ (.015) once daily. Posterior pituitary extract, 4 minims, was given daily for twelve days. This reduced the intake and output of fluids to approximately one-half of that previously reported. He complained bitterly of the injections and they were discontinued. Subsequently posterior pituitary powder was sprayed into the nares with an epinephrine nebulizing atomizer. This was without any noticeable effect on the diabetes insipidus.

Measurements made on Spetember 21, 1940, showed that the patient had grown ½ inch (1.27 cm.).

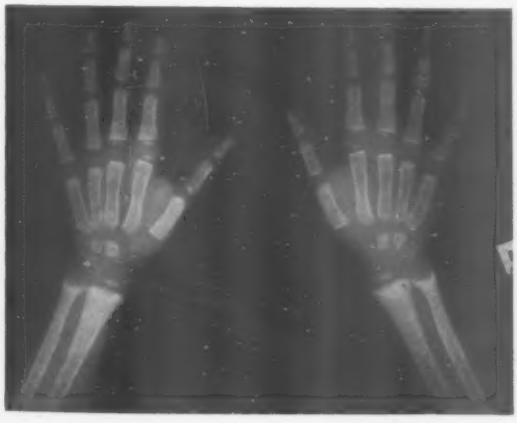

Fig. 6. Showing retarded development of the carpal and metacarpal bones and rickety cupping of the radius and ulna.

Fig. 7. Showing retarded development of the long bones of the lower extremities with extensive changes about the diaphyseal ends of the bones.

The urine continued to show 3 plus to 4 plus albumin with 10 to 15 erythrocytes per low power field.

Because the prognosis of these cases is so poor, as noted in Mitchell's review[64] and because reports in the literature (McCullagh and Rossmiller, Silberberg and Silberberg, Webster and Hoskins) tend to show that testosterone proprionate stimulates osseous development, it was decided to implant pellets of testosterone proprionate. It was explained to the parents that the treatment might produce, with its other effects, precocious sexual development. They consented readily to the suggested treatment and accordingly on September 7 four

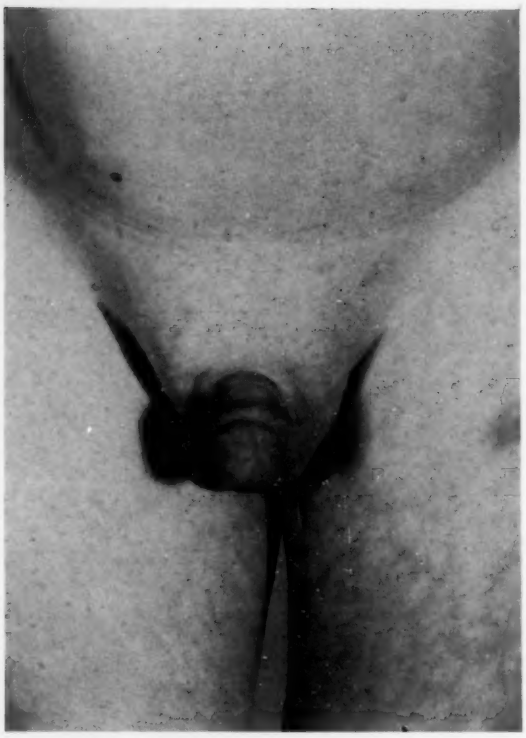

Fig. 8. Enlargement of the penis following implantation of testosterone propionate pellets.

pellets of 75 mg. each (total 300 mg.) were implanted in the right lower quadrant. On November 23 the mother stated that he no longer complained of headaches. The penis seemed larger and a small amount of pubic hair appeared (Fig. 8). His height had increased 1 inch (2.54 cm.) since September but his weight only increased 1½ pounds (0.7 kg.). There was no change in the intake and output of fluids; for example on November 21, 1940, his intake was 140 ounces and his output was 124 ounces.

On April 3, 1941, it was noted that the genu valgum was more marked (Fig. 9). The pubic hair had disappeared. Thyroid substance had been taken continuously since July 13, 1940.

Roentgenograms of the knees, wrists and forearms were made on July 2, 1941, and compared with those of a year ago. These were reported as follows:

"The knees, legs, wrists and forearms were re-examined and there are again demonstrated the extensive rachitic changes previously described. There is still very definite delay in the osseous development. There is some progression in the age development as well as in the linear growth, the former corresponding to a child of two years." (Fig. 10 and 11).

On August 1, 1941, his blood pressure was systolic 80 mm., diastolic 26 mm. His weight showed a 3 pound increase (1.3 kg.) to 29 pounds (13.2 kg.). There was no change in the diabetes insipidus, and the urine continued to show 2 plus to 4 plus albumin with approximately the same number of erythrocytes (5 to 8 per low power field). The specific gravity remained low (1.001 to 1.006). There has been no noticeable change in the blood calcium, phosphorus or phosphatase. The genu valgum continues to increase.

Since the beginning of treatment he has grown 2 inches (6.3 cm.) (July 8, 1940—33.5 inches, 80 cm; August 1, 1941—36 inches, 91.44 cm.). His span has increased 2¼ inches (5.7 cm.) during this time. His weight is practically stationary.

On September 11, 1941, the hemoglobin was

Fig. 9. Increase in height and increase in genu valgum are shown, the latter reducing the height as measured.

79 per cent, erythrocytes 4,080,000 per cu. mm. The urine contained 4 plus albumin. The measurements have not changed except that his height is apparently 1 inch (2.54 cm.) shorter (35 inches, 58.4 cm.). This is of course due to the increased genu valgum—the span being 2 inches (5.7 cm.) more than at the beginning. The testes and genitals remain the same. Walking is increasingly difficult.

On pitressin tannate* there was a reduction in the intake and output of fluids as follows:

	Intake Ounces	Output Ounces
September 6, 1941	87	74
September 7, 1941	74	68
September 8, 1941	76	69
September 9, 1941	70	60
September 10, 1941	72	66

There was a noticeable increase in linear growth in a period of one year but the interpretation is somewhat difficult for several reasons. First, there is a natural increment of growth but against this it must be said that he had never grown this much in any previous year; second, he received thyroid substance throughout the period of observation and he grew ½ inch during a short period previous to the implantation of the testosterone proprionate pellets.

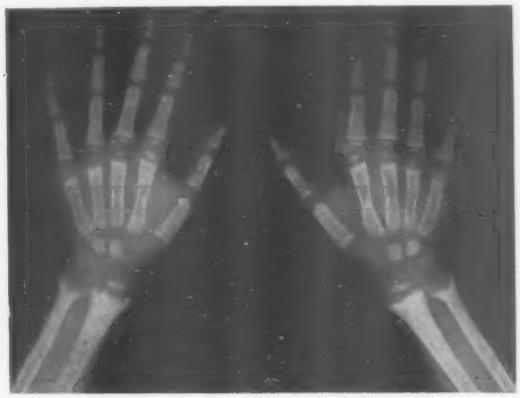

Fig. 10. Increase in development of the metacarpal and carpal bones but the cupping of the diaphyses is also increased.

The roentgenogram taken a year after treatment was begun reveals that there has been some progress in osseous development and would be commensurate with the linear growth. But that there has been no arrest in the progress of the rickets is shown by the fact that the genu

Fig. 11. Increase in linear growth of the lower extremities with increase of genu valgum and rickety changes.

Fig. 12. Pyorrhea and caries of the teeth.

* Intravenous pyelograms will be made while the patient is taking pitressin tannate. This may give a better outline of the kidneys.

valgum is increasing and the roentgenograms show no improvement in the rickets. The gums show pyorrhea and caries is present (Fig. 12). He seems somewhat more mature than a year ago. More recently there has been a more marked reduction in intake and output of fluids on the continued use of pitressin tannate. The average daily intake over a period of eighteen days was 67 ounces (2,010 cc.) and the output 61 ounces (1.830 cc.).

DISCUSSION

The outstanding features of this case are: Dwarfism associated with an osseous disturbance commonly called renal dwarfism or rickets; disturbance in kidney function with albuminuria; diabetes insipidus; progressive genu valgum and sexual infantilism.

It is unfortunate that retrograde pyelograms were not obtained since this would furnish more reliable information regarding the size of the kidneys. The possibility exists as shown by the diodrast method of study that the right kidney is either absent or deformed.

Some of the cases of renal dwarfism which have been reported with the various theories as to the etiology will be reviewed.

Albright and his associates reported the case history of a girl aged thirteen with persistent rickets and dwarfism. The serum calcium was normal, the serum phosphorus was low and a high serum phosphatase was present. This indicated that the condition was rickets and not osteitis fibrosa. The condition was accompanied by massive calcium deposits in the pyramids of the kidneys, hyperchloremia and a low serum bicarbonate level. The following sequence of events was proposed as the cause of the rickets:

1. Inability to make ammonia or to excrete an acid urine due to renal tubular disease;
2. Shortage of base with which to excrete mineral acids, notably chloride radicals;
3. Increased loss in the urine of calcium acting as a base;
4. Tendency to a low serum calcium level;
5. Secondary hyperparathyroidism to meet this tendency;
6. Hypophosphatemia;
7. "Low phosphorus" rickets.

Metabolic studies showed that calcium and phosphorus balances were improved by a low sodium chloride diet, more so by a mixture of sodium citrate and citric acid. The low sodium chloride diet and especially the citrate mixture produced an elevation of the serum carbon dioxide and a lowering of the serum chloride level. The condition is contrasted with "renal rickets" which is not rickets but osteitis fibrosa and which is associated with a form of kidney disease exhibiting notably phosphate and nitrogen retention. It is suggested, said these writers, that the condition here, characterized by rickets with hypophosphatemia, dwarfism, calcification of the renal pyramids, chloride acidosis, be designated nephrocalcinosis with rickets and dwarfism.

Amesse and Black report a case of a girl aged four years, whose mother was a morphine addict and had two roentgen-ray exposures to induce an abortion. The patient showed an astonishing failure physically and mentally. From the description their patient did not, in my opinion, have true renal dwarfism but may have had sequelae from the roentgen exposures of the mother.

Bader reports the case of a boy aged nine and a half who from infancy did not walk well, had weakness of the legs, polydipsia and stupor. Previously he had been bright and alert mentally. Marked genu valgum was present. High non-protein nitrogen, acidosis, decreased blood calcium and increased blood phosphorus were some of the laboratory findings.

The postmortem examination showed hypertrophy of the left cardiac ventricle, toxic necrosis of the liver, progressive atrophy of the glomeruli and tubules of the kidney with fibrous tissue replacement.

The second case was a younger brother who had polydipsia, secondary anemia, weakness, and was stunted in growth. The blood nitrogen was increased. Roentgenograms showed rachitic changes in the epiphyses and decalcification of the skeleton. Bader thought the second case was of the same type as the brother. He was of the opinion that the cause of renal dwarfism is obscure. Bader believed it to be due to a slowly progressive fibrosis of the kidneys limited to interstitial tissue beginning in early life with more tendency to produce changes in the systemic blood vessels than is the case with other forms of interstitial nephritis. He reported on 5 cases examined at postmortem and found that they were all of a similar type, namely,

small kidneys, the surfaces only slightly granular or irregular, the bulk of the changes were singularly limited to the interstitial tissue and these changes were progressive. The heart is usually normal or it may show a little hypertrophy of the left ventricle. The thyroid, suprarenal and pituitary glands were normal. The blood pressure in most cases is normal. The facial aspects showed an unhealthy, earthy pallor but no marked anemia was present. Intelligence was quite normal. Headaches were complained of but were not severe.

Most cases were small in stature from birth but this was more noticeable after the patients were nine years old. Sexual development was usually lacking but it may be present in some cases.

The most interesting point in regard to the bone deformities was the age at which genu valgum developed—ten and a half to seventeen and a half years and it usually developed quickly.

Brull and his associates studied the pathogenesis of 3 cases. They were interested in the interrelationship between the kidneys, parathyroids, phosphorus and bone metabolism. One of the cases showed a hypocalcemia and an elevated blood phosphorus. Cryptorchism was noted in one case associated with feminine skin texture. Necropsy in this case showed hypertrophy of the left ventricle and small atrophied kidneys with cysts. The second case presented kyphoscoliosis, high phosphate retention and acidosis. "The authors believe that the following factors produce or contribute to osteoporosis: (1) a mineral deficiency in the food and a (2) vitamin D impairment, connected with insufficient food ingestion due to pronounced anorexia; (3) lack of phosphorus and calcium fixation in the bones, arising from overactivity of the parathyroid glands, which in turn is due to phosphate retention, and (4) high acidosis. The relative involvement of each of these factors needs to be established in every case. The view that overactivity of the parathyroid glands reacting to phosphate retention is essentially responsible is not sufficiently demonstrated."

Brailsford expressed the opinion that slipping of the epiphyses of the head of the femur in adolescents is due to disorganization of the metaphyseal tissue which destroys its capacity to withstand the static strains or the trauma to which the normal joint is subjected without harm. Renal rickets is the cause of this disorganization of the metaphysis in some cases, and should be excluded before any operative measures are adapted. The roentgenographic appearance of renal rickets is almost diagnostic; the change may not be seen in one joint. He recommended urinalysis in all cases of slipping epiphyses.

Brockman compared the changes found in renal rickets and the usual type of rickets. He said it appears that chronic interstitial nephritis has always been in existence in these patients for a long time before they develop and have deformities. These changes are progressive and appear in some bones before others. It is reasonable to suppose that they are in some way dependent upon the failure of the kidneys to carry out their function.

Bates reported a case in a girl who menstruated at the age of six years. He thought that this represented pituitary involvement. Death was due to pericarditis and uremia. Both kidneys had irregular nodular sclerosis and each weighed 1 ounce. The left ureter was enormously dilated, the diameter being $\frac{3}{4}$ inch. There was a persistent thymus. The pituitary was small and flattened. The parathyroids were not enlarged. The uterus and ovaries were small. There were no rachitic changes in the bone. Microscopically the pituitary showed excessive colloid.

Cockayne and Lander reported a case in a boy of ten years. At postmortem the kidneys were smaller than normal and had a complete loss of cortical pattern. The bones showed thickening of the epiphyseal cartilage and an excessive amount of osteoid tissue. They were of the opinion that the bony changes were due to a disturbance of calcium and phosphorus metabolism. In the case reported the blood phosphate value was markedly above normal three years before bone changes became manifest.

Charnock stated that the clinical picture of renal rickets is that of a stunted, depraved child suffering from diminished renal function, severe acidosis and with an altered calcium and phosphorus metabolism.

He discussed three theories as to the etiology: (1) the renal theory; (2) the parathyroid hypertrophy theory; (3) the pituitary-diencephalon theory. He suggested that an overlap of all these theories may eventually clear the etiological difficulties.

Deroe and Brodny reported the case of a boy, aged sixteen, with undescended testis, urinary incontinence, genu valgum, a left inguinal hernia, and enlargement of the thyroid. His height was 56 inches (142 cm.). The values for blood calcium and phosphorus were normal. At postmortem the kidneys were small with dilated pelvis and the ureters were extremely dilated. There was an obstruction by the posterior urethral valve. The testicles were small and atrophic—no spermatozoa were present. The parathyroids were enlarged.

Debré, Marie and Jammet listed six groups of renal rickets:

1. Dilatation of the ureters, pelves of the kidneys, malformations of the genitourinary tract, horse-shoe kidney; absence of kidney; exstrophy of the bladder; vesicorectal fistula.

2. A group with arterial hypertension.

3. A group with metabolic disturbance of phosphorus and calcium metabolism. Genu valgum is present. Diffuse hyperplasia of the parathyroids is found. Calcification in various areas of the body.

4. A group associated with chronic interstitial nephritis, albuminuria and protein metabolism disturbance.

5. Congenital malformation of kidneys (1 of their 2 cases belonged to this group with a congenital lesion of the heart, congenital rectourethral fistula, optic atrophy, familial type as observed by Silberstern, associated with pituitary-diencephalon disturbance).

6. A group associated with glucose metabolism disturbance, alimentary glycosuria, acidosis resulting in calcium disturbance and disturbance in osseous development. Glycosuria and acetonuria are found.

It is obvious that there is no sharp distinction between these groups as outlined by the authors, and many cases show various combinations of congenital and acquired disturbances. Groups 1 and 5 seem to be the same. Danis and Rossen reported on 2 cases who were brother and sister. They expressed the opinion that a possible hereditary familial factor might be present.

Elliott from his studies was of the opinion that there exists a form of rickets developing in childhood in association with and apparently as a result of chronic nephritis. Other causes of persistent renal insufficiency such as congenital cystic kidney and double hydronephrosis may effect the same results. The bodily development is markedly retarded and when the patient survives beyond the age of puberty, sexual infantilism may exist. High blood nitrogen and uremia are common. Death usually results from kidney insufficiency.

Ellis[23] recorded a case in which bony changes of renal rickets appeared in a previously healthy child who contracted a severe nephritis. It may be, he said, that the acute attack of nephritis occurred in kidneys already diseased and so unmasked or hastened the onset of the symptoms of renal rickets.

Ellis[22] called attention to the importance and frequency of other abnormalities of the urinary tract in cases of renal dwarfism. He suggested a disorder of the neuromuscular mechanism controlling the urethrovesical sphincter as the responsible factor.

Firestone reviewed the features of the disease and differentiated the various endocrine types of infantilism and conditions simulating renal dwarfism. He was of the opinion that the retardation in appearance of the secondary sex characteristics was probably due to a secondary involvement of the pituitary gland which in turn acts on the other glands. The main problem with reference to the etiology was whether the finding of hyperplasia of the parathyroid was primary or secondary.

Fanconi reported 3 cases with nephritis, glycosuria and hypophosphatemia. The lesions were found in the tubules of the kidney.

Gittleman and Pincus stated that during childhood chronic glomerulonephritis of long standing has been recognized as an etiologic factor in the production of rachitic-like changes in the long bones. They reported a case associated with dwarfism, glycosuria, ketonuria, lipiuria, albuminuria and chronic acidosis.

Studies carried out indicated that the pancreas and the pituitary were the only glands of internal secretion which showed some evidence of dysfunction. It manifested itself in a disturbance of carbohydrate and fat metabolism resulting in chronic ketosis and acidosis, hepatomegaly, glycosuria and dwarfism. The acidosis was probably responsible for the chronic hypophosphatemia and the rachitic changes in the bones.

Graham and Oakley reported 2 cases treated with sufficient alkali to restore the alkali reserve to within normal limits and at the same time with large doses of vitamin D and A. The general condition improved, they grew in height and gained in weight, the state of the kidneys

was slightly improved, the anemia was little altered, while the condition of the bones was greatly improved.

György reported 3 cases, 2 of which came to autopsy. He was of the opinion that the condition was nephrogenic in origin.

Hamperl and Wallis reported 2 cases which had clinical and pathological anatomical studies. The first case in whom congenitally defective kidneys could not be excluded was that of an outspoken renal dwarfism. Death was due to uremia. In the second case, chronic interstitial nephritis and latent tetany were present. The dwarfism with bone changes was indistinguishable either clinically or pathologically from rickets. The authors were of the opinion that the disturbances occur at the same time; in other words, both conditions are the result of the same etiologic agent or agents.

Howard expressed the view that the disease is secondary either to unexplainable congenital defects or obstructive lower urinary tract pathology.

Hunt believed that infection plays a major rôle in the production of the disease. He quotes Fletcher to the effect that the disease dates from intrauterine existence. Hunt said that all cases show small kidneys at postmortem. The cardinal symptoms present are referable to retarded development and to the renal pathological changes.

Nye stated that the only similarity between patients with renal rickets and saturnine renal dwarfism is that they are both dwarfed.

Karelitz and Kolomoyzeff reported a typical case that had been observed for eighteen months. They concluded that the parathyroids contributed to the disease.

Karshner autopsied a case which showed chronic interstitial nephritis and small contracted kidneys, general anasarca, cardiac dilatation, adherent aortic cusps, atheromata of the aorta and endocardium, a large fibrous spleen, fatty liver and severe active rickets of the bones. The organs of internal secretion were negative.

Kennedy from his studies concluded that the so-called "woolly" type of renal rickets resembles hyperparathyroidism. He said that the hyperplasia of the parathyroid glands observed in renal rickets is not conclusive evidence that increased parathyroid activity plays a predominant part in this condition since it is also observed in other skeletal diseases such as true rickets, multiple myeloma, and metastatic carcinoma. The parathyroid hyperplasia is considered as a secondary phenomenon in renal rickets rather than a primary factor in the etiology of the disease.

According to Lathrop the renal lesions are of such a nature that they in some way influence the general metabolism. There is a disturbance in the normal relationship between calcium and phosphorus content in the normal body fluids, which results in a profound alteration and delay in the normal body development. Possibly this disturbance is primarily a phosphate retention, which appears to depress the calcium concentration of the blood. Aside from the defective osseous development and its consequence, the case runs the course of a severe chronic nephritis with maximal nitrogen retention and curiously with little effect on the cardiovascular system. During the late stages, he said, a rather severe acidosis appears, attributable in part to the phosphate retention.

Lightwood reported a case in a male, aged seventeen months, prematurely born of healthy parents. The roentgenological studies showed rachitic changes. Albuminuria, high blood calcium phosphorus and nitrogen were present. The brownish-yellow skin was an important clinical feature. His patient died at the age of twenty-seven months with calcinosis and widespread arterial degeneration; the cause of the latter was quite unknown, nor was its relation to the disordered calcium and phosphorus metabolism understood. An extreme obliterative endarteritis predisposed to local tissue degeneration and a slightly excessive intake of lime, in the virtual absence of normal bone growth, may have been a factor in the deposition of calcium in the damaged arteries, degenerating tissues and in the bones. The calcinosis in this case was not due to excessive intake of vitamin D. Commenting on other cases in the literature, Lightwood suggested that this rare group to which his case belongs be given the descriptive clinical title of "calcinosis with arterial degeneration."

Lignac has stated that all cases show serious affections of the kidney—not all being the same type. In some, serious albuminous degeneration is present, in others there exists an acute nonpurulent pyelonephritis, and in others incompletely developed kidneys are present.

Stunted growth and development in early youth is conspicuous. Fully developed rickets is

always present. The term renal rickets or renal dwarfism implies that in these cases the affection of the kidney causes the rickets and dwarfism.

According to Maddox the average age of onset, as collected from the cases in the literature, on their first coming under observation was seven years. The first appearance of genu valgum is commonly between twelve and fourteen years. Some have reported them as early as sixteen months. Among 72 patients there were 39 males and 33 females.

As symptoms Maddox listed the following:

1. Polydipsia was noted in 40 of 72 cases and was especially prominent under three years of age—when the child tends to cling to all liquid diet.
2. Polyuria.
3. Development is retarded. Slow epiphyseal growth is complemented by the reduction in height caused by the severe degree of genu valgum. Intelligence is fair, being proportional to the extent of the toxemia and to the degree of interference with education caused by the invalidism. The facies and expression are often mature.
4. Pain in the knees was noted in 5 per cent of cases, probably arising from ligamentous strain.
5. Symptoms of uremia, such as anorexia, constipation, vomiting and convulsions are present in varying degrees.
6. Infantilism in some degree, but never complete, is usually apparent in cases beyond the age of puberty.
7. Pallor or a pale dry, wrinkled skin—absence of sweating. The blood count shows secondary anemia. Pigmentation appears more common than is usual with nephritic adults.
8. Cardiovascular hypertrophy is a very variable occurrence.

Maddox lists the bone deformities as follows:

1. Genu valgum is an important sign and is best seen in the older children or in younger patients only after walking has commenced. Synchronous curving of the femora and well marked epiphyseal enlargement.
2. Frequently no changes in the skull.
3. Changes in the thorax are of the same order or occur in nutritional rickets, for example enlargement of the costochondral junctions, Harrison's sulcus and pigeon breast.
4. Malacia of the long bones.

Mitchell in a comprehensive article reviewed the literature on renal dwarfism up to the year 1930. From his studies he stated that the terms renal dwarfism or renal nanism are employed to designate the small stature and stunted growth almost invariably accompanying chronic kidney disease in early life. The term renal infantilism denotes the lack of sexual development which may be a feature. The term renal rickets obviously applies to a special group of symptoms and effects which are described in some of the cases. Renal pseudo-rickets has been the term occasionally employed.

Mitchell expressed the opinion that credit for first recognizing the association of chronic kidney disease with changes in the bones should probably be given to Lucas who described the occurrence of late rickets with albuminuria in 5 patients and asserted that the phenomena of late rickets and albuminuria were too frequent to be matters of chance.

Mitchell reviewed a series of 78 cases of renal dwarfism having clinical or roentgenologic evidence of abnormal bone changes. A partial summary follows:

In 32 cases the age of onset averaged five years and two months. Of 74 cases with bone changes whose sex was stated there were 39 males and 35 females. None were reported in the colored race. Most of the cases reported were from England where the colored population is small. There was marked caries of the teeth in 6, delay in eruption in 3. Some authors found that the children with renal rickets were exceptionally bright. In 16 of 25 cases who had reached or passed the age of fifteen, there was delayed sexual development. Lack of menstruation, imperfect development of genitalia and breasts; scanty or absent pubic or body hair and childlike voice.

Sixty-four had polyuria. In 57 instances polydipsia was noticed at the time of weaning. Forty-nine complained of headache and this symptom came later than the polydipsia and polyuria. Vomiting with headache was not infrequent. Uremia was present in 62 patients. Convulsions were associated in the majority of cases with uremia. There was a hemorrhagic tendency in 20 patients. Disturbance in vision was found in 16 cases. Twenty-eight showed ophthalmological signs of uremia. Secondary anemia was present in all cases. Pigmentation of the skin was seen in 30 cases. Brownish, yellowish, gray-yellow, or gray-green, dirty sallow, bronzing was the way this was described. Inelasticity, dryness, coarseness of the skin, and lack of perspiration was noted in some cases. Of

circulatory symptoms, 13 showed dyspnea and palpitation. Cardiac enlargement was found in 46 patients.

Arteriosclerosis was reported in 24 cases. The superficial vessels were hard, cord like and rigid. Thirty-three had increased blood pressure. In 3 of the reported cases renal calculi were found. Changes in the suprarenal bodies have been described but there is no conclusive evidence that these are concerned in any way in the pathogenesis of the bone changes in renal rickets.

Genu valgum was present in 31 patients, and nine years was the average age of onset.

Various types of kidney changes were found in 78 cases. Several had horse-shoe kidneys; absence of one and cystic changes in the other; single horse-shoe structure, cystic changes in the other; reduction of kidney substance and defective kidney development.

The average age of death was given as nine years and nine and a half months. The earlier the onset of symptoms, the worse the prognosis.

The etiology of renal dwarfism could be summarized, according to Mitchell, as follows:

In a type of nephritis characterized by a relative or absolute inability of the kidneys to excrete the waste endogenous phosphates from the body, there exists considerable evidence that such waste phosphates may be excreted through the intestinal mucosa instead of from the kidneys. It has been repeatedly demonstrated that an increased concentration of phosphates in the food—that is, in the intestinal contents—may interfere with the absorption of calcium, presumably through the formation of insoluble calcium phosphates. A hypothesis is offered that in renal rickets such a shift of the excretion of endogenous phosphorus to the intestines occurs, and that the concentration of phosphorus in the intestine thus increased so blocks the absorption of calcium from the food that the child suffers a true calcium starvation. Mitchell said, "It is of some importance to state that of ten instances in which cystic changes or greatly dilated tubules were found in the kidneys at necropsy there were nine in which clinical or roentgenological evidence of bone changes had occurred."

Meier and Thoenes reported a case in which infantilism and dwarfism were present with chronic glomerulonephritis, atony of the ureters, enlargement of the kidney pelves, atony of the bladder, calcium deficiency of the whole skeleton, changes in the epiphyseal development, infractions and deforming joints. At autopsy, coxa vara, arthritis deformans, a small prostate and sclerosis of the coronary arteries were the important features.

Mikulowski, who reported a case, believed that the "endocrine function of the kidney was interfered with producing the clinical picture."

Miller and Coe in reporting their case were of the opinion that the renal insufficiency leads to an acidosis which is supposed to cause a mobilization of calcium from the bone, resulting in decalcification.

Nichols and Shiflett said that most of the theories are based on a disturbed calcium-phosphorus balance resulting from the inability of the kidneys to excrete endogenous phosphates.

Pappenheimer stated that the parathyroid glands react to a loss of function of renal tissue by an increase in volume; roughly proportional to the severity of kidney damage. There is no direct evidence that the hyperphosphatemia is the chemical incitant to hyperplasia, and we are confronted with the fact that such hyperplasia occurs with equal consistency in low phosphorus rickets. On a diet containing adequate calcium and phosphorus, the parathyroid hyperplasia induced by partial nephrectomy was only exceptionally accompanied by slight osteofibrotic changes in the bones and these were never of an intensity comparable to those observed in primary hyperparathyroidism or in renal rickets. On the other hand, when rats with experimental renal insufficiency were placed on a low calcium diet the resulting skeletal lesions were greatly intensified. On a very low calcium intake they took on the character of florid rickets indistinguishable from that produced by the low phosphorus rachictogenic diets. With moderate addition of calcium, the picture was rather that of an osteitis fibrosa.

Attention has been drawn to the frequency of accompanying hydronephrosis and dilatation of the ureters, sometimes associated with vesical hypertrophy. In some cases anatomic explanation for the renal obstruction has been found (phimosis, valve-like folds in the urethra). In other cases, no organic structure has been discovered, and a disturbance in sphincter control has been assumed.

Parsons made the statement that treatment of the condition by ultraviolet irradiation is contraindicated and evidence is produced to show that such treatment aggravates the bone changes.

Paterson reported 2 cases, one had a large-sized head, the hands and feet were deformed at birth; the second case had had genu valgum since the age of two and a half years.

Platt and Owen's case had hard plaques of calcium in the skin. The kidneys each weighed ¾ ounce. Interstitial fibrosis, dilatation of the tubules and calcification of medium-sized and small arteries were present. The parathyroids were normal. The brain was not removed.

Price and Davie gave the concept of renal rickets as a syndrome representing the common ground of overlapping of hyperparathyroidism, on the one hand, and of chronic renal damage, on the other. They felt that this is the most satisfactory explanation in the present state of our knowledge. In a limited autopsy in their case the four parathyroids were hyperplastic and the one examined kidney was greatly reduced in size.

Roberts' case had a marked dilatation of the urinary tract and hypertrophy of the bladder. The urinary retention appeared to occur at the level of the urethrovesical sphincter. Microscopically the kidneys showed a great reduction of the glomeruli. Of particular interest were the changes in the pituitary gland and the hypothesis was suggested that the dwarfism may be due to a secondary effect on the pituitary of some product of altered metabolism as a result of the long-standing renal insufficiency. Definite microscopic changes in the bones of the vertebral column were described.

Russell and Barrie reported 3 cases in which advanced Bright's disease was associated with a disturbance of cystine metabolism. In the first two examples, cystine was stored in the reticulo-endothelial system, the deposits being visible to the naked eye as opaque ochreous flecks and streaks. In the third example, cystinuria and stone formation were recognized in early childhood; no cystine was found in the tissues at necropsy. They believed that the association of cystine metabolism disturbance in association with renal rickets cannot be dismissed as coincidental. They were of the opinion that the primary disturbance is due to renal injury. Experimental work on rats and rabbits showed that the oral administration of cystine results in renal injury.

Schoenthal and Burpee said that all of the investigators think that the primary cause of the diminished deposition of calcium in bone is the inability of the kidneys to excrete phosphate. They felt that two types of renal rickets may be distinguished; one due to congenital malformation of the kidneys or urinary tract; the other is due to a chronic renal insufficiency of the character of a chronic interstitial nephritis becoming manifest later in childhood.

Replacement of depleted base, calcium and phosphorus is the logical method of treatment although the effects are but temporary unless treatment is continued. This may be accomplished by the administration of an alkaline ash diet, together with calcium acetate.

Salvesen treated his case with calcium lactate, cod liver oil, ultraviolet irradiation. No dwarfism to any extent was present.

Smyth and Goldman, from a study of their case, felt that parathyroid dysfunction was present. Calcium was deposited in the joints. According to these authors the underlying pathological condition, in their case, was probably a congenital partial urethral obstruction with hydronephrosis. On this was superimposed a streptococcic infection which was manifested by clinical signs of severe diffuse nephritis. The retention of acid phosphate constituted the first important change in the chemical constitution of the blood.

It was suggested that stimulation of the parathyroids by the high level of phosphorus in the blood resulted in dwarfism and demineralization of the bones.

Shelling and Remsen's case had four enlarged parathyroids. They said that, strictly speaking, the term renal rickets should be applied only to cases of rickets from chronic renal disease. Renal infantilism apparently shows neither rickets nor renal disease—the infantilism is probably due to involvement of the anterior pituitary by the same disease process which affected the posterior portion and caused the symptoms of diabetes insipidus.

They reported a case in which increased amounts of parathyroid hormone in the blood were demonstrated antemortem and four enlarged parathyroids were found postmortem. They also suggested that the parathyroid hyperplasia was caused by phosphate retention, and the demineralization in the skeleton is due among other factors to the necessity of excreting the retained phosphate as the insoluble salt of calcium in the bowel, to the compensatory secretion of increased amounts of parathyroid hormone and possibly also to the chronic acidosis. The underlying cause of the renal impairment in their patient was a bilateral hydronephrosis, probably the result of an obstruction

in the genitourinary tract. The chemical symptomatology, the roentgen appearance of the bones, the metabolism of calcium and phosphates and even the presence of increased amounts of parathyroid hormone in the blood in the case described were indistinguishable from those seen in osteitis fibrosa of the osteoporotic type, complicated by impairment of renal function. The differential diagnosis rests largely on the chronological history as to the onset of renal failure, on the presence or absence of nephrolithiasis or nephrocalcinosis (present in hyperparathyroidism and absent in renal rickets), and on the presence or absence of congenital anomalies of the genitourinary tract.

Spence listed the symptoms and signs of renal dwarfism. He stated that fractures are common when the dwarfism and bony changes are extreme.

Swart listed the diseases that may be confused with renal rickets: hyperparathyroidism, late rickets, juvenile Paget's disease and early osteomalacia. The question of etiology was left open.

Smellie gave as his opinion that in the active stages of renal rickets the blood phosphorus is markedly raised, whereas in healed renal rickets the figure approaches normal. That this is the result of exacerbation and remission of the kidney condition seems obvious. Administration of vitamin D by increasing phosphorus absorption will aggravate the condition.

Vogt was of the opinion that the etiological diagnosis of renal rickets cannot be made from roentgenograms alone. If the bone lesions are atypical or if the patient is beyond the age when rickets occurs, suspicion should be directed toward the kidneys as a possible cause.

Watson-Wemyss' case died with uremic convulsions and at autopsy the kidneys were reduced in size and microscopically there were noted changes typical of arteriosclerotic kidney. The heart was enlarged and the right suprarenal gland was notably enlarged.

Webster reported 2 cases; one, a boy aged eighteen months, had a dilated posterior urethra, dilatation of the ureters and hydronephrosis. The second one, a boy aged twelve, had a small left kidney which was devoid of renal parenchyma. There was a dilated left ureter ($\frac{1}{2}$ inch–1.27 cm.); the right ureter was also dilated. There was approximately one-sixth the amount of renal tissue, a true agenesis of the kidneys.

Wheeler and Thompson's case was in a child, aged six, with a positive Wassermann reaction. They thought that the condition could be accounted for by congenital syphilis.

From his studies of renal dwarfism, Chown came to the conclusion that the disease is the result of a pituitary-diencephalon disturbance. He said: "The argument in proof of the thesis that a lesion of the pituitary-diencephalic mechanism is the primary cause of the symptom complex called renal rickets is then as follows:

"1. Malformation of the pituitary has been found in these cases;

"2. The associated symptoms of the dwarfing infantilism and urinary tract dilatation can be caused by such a lesion;

"3. The nephritis is not primary but is secondary to an abnormal mineral metabolism, itself the result of faulty bone growth;

"4. The faulty bone growth therefore not being due to the nephritis, and the remaining symptoms being due to pituitary-diencephalic disease, it is to be presumed that the bone disease is due to the same cause."

He further stated that there are three theories given as the cause of the symptom complex:

1. Chronic deficiency due to renal failure;
2. Hyperparathyroidism either primary or secondary to renal failure and,
3. Pituitary-diencephalic malfunction. The cause of the damage to the kidneys remains obscure.

Implicating the pituitary-diencephalon fits well with the observed facts, which he said, are difficult to explain on the basis of primary chronic nephritis.

The polyuria, the dwarfing, the infantilism, the urinary tract dilatation can be caused by such a lesion. The first three are well recognized as of pituitary origin. Dilatation of the bladder sometimes occurs following injury to the spinal cord and may be relieved by resection of the presacral nerve. Sympathetic and parasympathetic centers exist in the diencephalon. Therefore worn or ill-made parts in this mechanism might produce not only diabetes insipidus, dwarfing (growth promoting factor of the anterior pituitary), infantilism (sex stimulating factor of the anterior pituitary), but also urinary tract dilatation (diencephalon). He explained the rickets on the basis of calcinuria and phosphaturia.

In 1928, discussing Lathrop's case I said: "Lathrop reports a case of renal dwarfism in

which there was a marked retardation of development of the epiphyses, especially at the wrist. The kidneys were both distorted pieces of tissue which externally hardly resembled kidneys. No mention is made of the state of the pituitary. Some of the symptoms while possibly due to the malfunction of the kidneys are suspiciously like hypofunction of the pituitary, viz., late onset of menstruation, no secondary sex characteristics, polydipsia, polyuria, dwarfism, retardation of ossification. Even the drowsiness, while most likely renal in origin is like pituitary narcolepsy."

The concept of a pituitary-diencephalon disturbance would, in my opinion, be the correct one and data will be presented to show this hypothesis is a logical one, albeit one that differs somewhat from Chown's and others.

Throughout the reports of the cases it is noted that developmental defects of the kidneys and urinary tract are important features of the disease. It will be shown that the pituitary gland is responsible for the genitourinary tract defects in that malformation or malfunction of the pituitary causes malformation of the genitourinary tract. There is no need to assume, as Chown did, that dilatation of the kidney pelves and bladder is the result of a nervous disturbance in the diencephalon.

The best evidence that a defective pituitary can cause malformation of the genitourinary tract is found in the anencephalic fetus. It is now quite definitely established that anterior cerebral defects are accompanied by pituitary anomalies.

Kraus reviewed the evidence of this association. He stated that in anencephaly there is found regularly a developmental anomaly of the pituitary, the anomaly varying in different cases.

Browne called attention to the condition of apituitarism associated with anencephaly.

Covell studied 32 anencephalic fetuses and concluded that: the pituitary is extremely variable in weight, being less than normal; the pars nervosa is lacking in the majority of cases; the pars intermedia is variable as to both occurrence and volume.

Barlow, Kiyono, Kohn, Mauksch, and many others, have reported on the association of brain defects and anomalous development of the pituitary.

That the pituitary defect is accompanied by suprarenal cortex defects has been pointed out by these same writers, and in 1929 I reviewed a part of the literature on this association.

Experimentally it has been shown by Smith and others that hypophysectomy results in atrophy of the suprarenal cortex and there also results an atrophy of the kidneys.

Davis in his study of malformations in the kidneys and ureters concluded that the genital and urinary organs are never quite completely separated even in the female of the human. Co-existing abnormalities of the genital and urinary organs are frequent. He reported cases of dilatation of the urinary bladder and kidney anomalies associated with hydrocephalus. The anomalous development and aplasia of the suprarenal cortex, urinary organs and genital organs has been frequently reported.

Morel reported a case of hyperostosis frontalis interna associated with agenesis of the kidney. In this disease a pituitary disturbance has been assumed by most writers (literature by Knies and Le Fever).

Kraus has written extensively on the pituitary changes produced by chronic increased intracranial pressure. His work was based on 150 cases of this condition. Among the causes listed as producing it he mentions chronic hydrocephalus internus. Necrobiotic changes take place in the pituitary and particularly in the stalk of the gland, so that a morphologic substrate is produced that results in a typical diabetes insipidus.

Hydrocephalus with its increased intracranial pressure may produce degenerative changes in the pituitary and the latter, as has been shown in these cases, may be accompanied by genitourinary defects. Kidney malformations, agenesis, dilatation of the urinary tract, are all associated with the pituitary anomaly.

Such, then, are the conditions as seen in renal dwarfism and we have therefore a logical explanation for the pituitary and genitourinary pathology. Re-stated, the primary pituitary defect results in a secondary genitourinary defect.

In the case here reported extensive hydrocephalus was present and there was damage to the pituitary as shown in the roentgenograms of the skull as well as the definite clinical picture associated with hypofunction of the whole gland.

Notable features listed in practically all

case reports of true renal dwarfism are the defective development and smallness of the kidneys.

That a hereditary element was present in the case here reported seems likely. Shortness of stature was a dominant characteristic on the maternal side, the mother herself being but 58 inches (148.5 cm.) in height. Five maternal uncles and 4 maternal aunts were abnormally short in stature. In addition, one of the aunts had "chalky" teeth which indicates a poor bony structure. The father of the patient was tall and obese and would be classified as a hyperpituitary type. A duoparental pituitary disturbance was therefore passed on to the patient.

A nervous disturbance had been present on both sides of the family, namely, convulsions in the father as a child, and in the maternal aunt with "chalky teeth." It is not unlikely that the child (a brother of the patient) who died of pyloric stenosis had a central nervous disturbance (interbrain) such as that postulated by Rokitansky and Cushing for peptic ulcer. The mother said that this child acted just like the patient when he was born. The behavior of the deceased infant and the patient during infancy would perhaps indicate that the former suffered from the same condition.

Dyspituitarism on a hereditary basis was probably responsible for the pituitary defect. The development of the skull in these cases is of interest and the work of Mortimer furnishes additional information and support to this hypothesis.

This investigator reported on 494 dysplastic craniums in human beings. Sixty per cent of the patients who showed evidence of disturbance in cranial form and structure, presumably during the growth period, suffered subsequently at some time or other from a dyspituitarism that was recognized physiologically. This fact was taken to support the view that cranial dysplasia is probably produced by dyspituitarism and not by an autochthonous peculiarity of certain tissues in response to a normal secretion from the anterior lobe of the pituitary gland. That the cranial deformity resulted in response to abnormal pituitary function is reasonable, the presumption being that those persons in whom dyspituitarism is physiologically recognizable today in whom cranial dysplasia also exists suffered also from a dyspituitarism at the time when cranial form and structure are most susceptible to hormonal influences. Mortimer was of the opinion that in cases in which a familial tendency to such deformity undoubtedly exists, a familial tendency to dyspituitarism may be suspected.

This latter statement is appropriate to the present case since it was pointed out that a familial tendency to dyspituitarism exists in the patient under discussion. Furthermore, in an article on retinitis pigmentosa the clinical observation was made on a series of 21 patients that a high arched palate was present in every one of them. This was taken as an indication that there was a close relationship between the embryological development of the hard palate and the anterior lobe of the pituitary gland, since the latter developed from the roof of the mouth and a disturbance in the embryological development of the pituitary would be reflected in the hard palate. The patient, as noted, had a high arched palate. Thirty of Mitchell's 78 compiled cases had pigmentation of the skin and it might be postulated that this was due to a disturbance in function of the pars intermedia. A discussion of the pituitary and pigment formation was given in the article on retinitis pigmentosa. Where total destruction of this portion of the pituitary exists one could hardly expect pigmentation of the skin but where it did exist, then by irritation of this lobe pigmentation would follow.

There were no reports of renal dwarfism in the Negro but as Mitchell pointed out, the Negro population of England where most of the cases have been reported is small. Nevertheless it is of interest that the Negro according to Freeman has a heavier pituitary than the Caucasian if the weights of the pituitary glands of persons of the same sex are compared.

Phylogenetically, then, this would favor

a better development of the pituitary in the Negro and therefore a less likely incidence of its maldevelopment.

Cushing called attention to a peculiar brownish pigmentation of the skin in patients having third ventricle tumors and so the defect in this area suggests that the pigmentation is a frequent part of the picture.

The influence of the thyroid substance on the osseous development in the case here reported is of interest and it seems that growth had already begun before the implantation of testosterone proprionate pellets. One interpretation of the failure of the pellets is that an active pituitary or at least a sufficient number of normal pituitary cells must be present to produce the changes in the bones and genitals. This would mean that bone growth is produced by the testosterone or sex hormone by way of the pituitary.

Some might argue that the dosage was sufficient to depress the pituitary and thus aggravate the condition. This possibility certainly exists.

The craving for lemons which the patient exhibited would indicate that citrates would be useful therapeutically. This is in line with the studies of Albright and his associates in which they prescribed a sodium citrate mixture and citric acid. Experimentally it has been shown that parathyroidectomized rats will select the water to which calcium has been added (Richter and Eckert) showing, therefore, a natural selection for a depleted and necessary substance.

Such natural instincts for deficient substances is probably Nature's way of overcoming the disturbance. Craving for sugar in the diabetic whose blood sugar is high is an indication that the cell protoplasm is unable to incorporate the sugar due to lack of insulin or other chemicals. In such instances the blood sugar merely passes by the cell protoplasm. So in renal dwarfism the bases in the blood stream are not utilized by the cells and these substances are excreted. It is tempting to speculate that the pituitary hormone or hormones are lacking in this disease and there is failure to utilize necessary substances for bone building. The excretion of these substances acts as an irritant to the congenitally malformed kidneys, resulting in nephritis and its consequences.

In this regard the work of Neufeld and Collip is of interest. These investigators found that "parathyroid extracts produced no effect on the serum calcium in rats, cats or dogs immediately following nephrectomy or ligation of the renal vessels or of the ureters. Re-establishment of urine flow in one cat by cutting the ligated ureters was followed by a normal parathyroid hypercalcemia. During anuria induced by posterior pituitary extract no parathyroid hypercalcemia was noted. Injection of parathyroid extract followed by repeated intravenous administrations of sodium acid phosphate to maintain a constant serum phosphate level prevented the customary rise of serum calcium. The evidence given does not suggest a direct effect of the parathyroid hormone on bone. These results rather favor the theory that the primary action of the parathyroid hormone is upon the excretion of phosphate by the kidneys."

The prognosis as has been shown is poor. Defective development of the kidney plus a subsequent nephritis makes the outlook hopeless. That inheritance is an important factor if not the most important one is shown in the present case.

The poor tone of the muscles in the patient here reported is shown by the distention of the abdomen, the marked pes planus, increasing genu valgum, and hyperextensibility of the joints.

SUMMARY

A case of renal dwarfism associated with diabetes insipidus is reported. Growth of the carpal bones and an increase in linear growth and height followed the use of thyroid substance. Testosterone proprionate pellet implantation produced an enlargement of the penis and a moderate temporary development of pubic hair. Roentgenograms of the wrists showed an increase in

development of the carpal bones. The rôle of the thyroid and testosterone proprionate therapy in the changes produced is difficult to evaluate because both were given at the same time and a control period of thyroid alone resulted in a growth of one-half inch (1.27 cm.) within a comparatively short time. This would suggest that thyroid substance alone was responsible for the osseous development. The genu valgum increased. Posterior pituitary lobe extract in the form of pitressin tannate reduced the intake and output of fluids to approximately half that taken previously.

A duoparental pituitary inheritance factor was present in the case reported and evidence was presented to show that the pituitary gland disturbance was responsible for the clinical picture. The high arched palate of the patient was taken as an indication that the development of the anterior lobe of the pituitary gland was disturbed since this lobe develops from the roof of the mouth.

A congenital dyspituitarism on a familial basis, as pointed out by Mortimer, was assumed to be responsible for the disturbance in cranial form and structure.

A congenitally deformed pituitary gland or an anomalous development of this gland is frequently associated with congenital cerebral defects such as anencephalus and hydrocephalus. Such a pituitary defect is associated with a secondary genitourinary tract defect in the form of kidney malformation, dilatation of the kidney pelves and the bladder. Agenesis of the suprarenal cortex is also usually present.

The factor of inheritance would seem to be the most important one in the etiology of the disease.*

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* Since this paper was written the patient died, on August 19, 1942. No autopsy was obtained. He died with signs and symtoms of uremia.

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EPIDERMOID CARCINOMA OF THE TIBIA

REPORT OF TWO CASES

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DIRECT invasion of a bone by squamous carcinoma is a rare condition as compared with the well known metastatic lesions. An epidermoid carcinoma is most frequently found in the bones of the skull and mandible, where the growth is believed to arise from islands of misplaced ectoderm (Hellner) with the overlying skin remaining intact.

In other parts of the skeleton, squamous carcinoma of the bone originates usually in a chronic ulcer of the skin or an epithelialized fistulous tract. This process is most apt to develop in the tibia because its overlying skin is close to the bone and is easily damaged by varicose veins or osteomyelitis. Tibial carcinoma has been chosen therefore as the topic of this discussion.

There are two types, etiologically, of invasion carcinoma of the tibia: (1) ulcer carcinoma, which arises within a chronic ulcer of the leg, and (2) fistula carcinoma, which originates in a fistulous tract or osseous sinus.

These two predisposing conditions, the ulcus cruris and the fistula, may persist for years without becoming malignant. Therefore, the development of a carcinoma might not be suspected in its early phase, when a complete cure could be accomplished either by amputation or by more conservative procedures. Fortunately, however, these tumors, even in an advanced stage, are characterized by a low grade of malignancy and, like other epitheliomas of the skin, hardly ever form distant metastases.

Despite the rare occurrence of epidermoid carcinoma of the tibia, I have seen at City Hospital an ulcer carcinoma (Case I) and a fistula carcinoma (Case II) within a period of three months. Since the early diagnosis is of great importance, the following report of cases and discussion of the disease is believed to be of interest and of practical value.

REPORT OF CASES

CASE I. *Ulcer Carcinoma* (No. 106746). C. M., colored female, aged sixty-six, laundress and cook, was admitted to City Hospital, Dermatological Division of Dr. Eller, in July, 1941, with the diagnosis of chronic ulcers of the left leg. The patient had suffered from varicose veins for more than thirty years and had worked always in a standing position. Small ulcers developed frequently in both legs, which healed on numerous occasions following the application of carbolic solutions and ointments. However, a recurrent ulcer of the leg, recently treated by a "paste," spread so rapidly that the patient had been unable to walk for the past two months. There had been an ever increasing discharge of purulent material.

The patient was transferred to the Surgical Services of Dr. I. Kross as soon as the roentgen examination revealed an extensive osteolytic process of the mid-shaft of the left tibia with a pathological fracture and periosteal thickening of the proximal one-third. On clinical evidence alone, the diagnosis of osteomyelitis had been considered, but this was not borne out by the roentgen findings which pointed rather to carcinomatous invasion of the tibia (Fig. 1).

The surgeons reported a widely ulcerated area of the anterior portion of the leg from below the knee almost to the ankle and extending posteriorly in the mid-portion. There was a foul discharge, and a few necrotic osseous particles were seen in the ulcer crater.

A disarticulation of the knee was performed under refrigeration anesthesia. The patient had an uneventful recovery and was discharged four weeks postoperatively.

Pathological examination by Dr. J. R. Lisa revealed a chronic ulcer of the skin eroding into the bone. The base of the ulcer contained nests of malignant epithelial cells with pearl forma-

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tions and chronic destructive and inflammatory lesions of the bone.

Case II. *Fistula Carcinoma* (No. 110337). M. A. McD., white female, aged seventy-six, was admitted to the Surgical Service of Dr. P. K. Sauer in October, 1941, with a recent fracture of the left tenth rib and a chronic ulceration of the left leg. The infection of the leg developed gradually following a contusion in 1932. Although the disease had become progressively worse throughout the years, the patient had neglected it because of discouragement due to unsuccessful skin grafts and other surgical procedures in the beginning of her illness. During the past six months she had lost about 20 pounds.

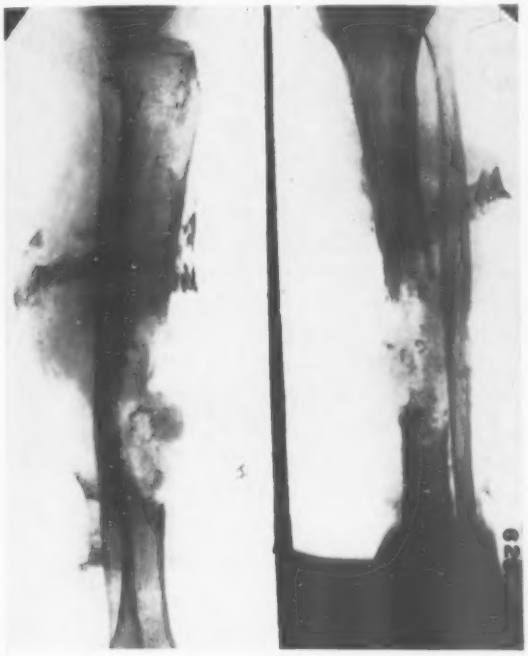

Fig. 1. Case I. Epidermoid carcinoma of the tibia arising from a recurrent varicose ulcer of the leg which has recently been treated by a paste. Note pathological fracture.

Inspection revealed a large ulceration of the anterolateral portion of the lower left leg, 15 by 8 cm., which extended to the bone. There was a profuse purulent discharge and sloughing necrotic tissue. The edges of the ulcerations were irregular, rolled, and indurated, and the tibia was partially exposed.

Roentgen examination of the left leg revealed an old osteomyelitis of the mid-shaft of the tibia. The periosteum was irregularly proliferated and

Fig. 2. Case II. Fistula carcinoma of the tibia arising from a chronic osteomyelitis which has been untreated for nine years. Note decalcification, rarefaction and surface erosion of bone.

Fig. 3. Case II four weeks later. Amputation specimen. Note marked progression of the osteolytic process and pathological fracture.

ossified and surrounded an involucrum with cloacae. There was marked surface erosion of the anteromedial portion resulting in a moth-eaten appearance, decalcification, and practically complete disappearance of sclerotic bone densities (Fig. 2). Because of these unusual roentgen findings, epidermoid carcinoma was strongly suspected, and a biopsy confirmed the diagnosis.

Within two weeks, there was distinct progression of the osteolytic process and development of a pathological fracture. Roentgenograms of the entire skeleton and chest did not reveal any metastatic lesions. In view of the advanced age and malnutrition of the patient, she was carefully prepared for an operation, and a disarticulation of the knee was performed two weeks later under refrigeration anesthesia. Following an uneventful recovery, the patient was discharged two months postoperatively.

Roentgenograms of the specimen of the leg illustrated further decalcification and destruction of bone with a pathological fracture of the tibia (Fig. 3). Pathological examination of the amputated leg by Dr. J. R. Lisa disclosed the origin of the cancer to be within the fistulous tracts of the bone. The edges of the cutaneous ulceration were not malignant.

COMMENT

The first case is of interest because the history of recurrent ulcers dated back more than thirty years. In the second case, there was a chronic osteomyelitis with the relatively short duration of nine years. In both instances, the malignant growth developed rather suddenly and progressed rapidly.

The first patient came to the hospital only after a pathological fracture had occurred. The second patient had lost 20 pounds during a period of six months and had noticed progressive oozing of the leg and progressive weakness; nevertheless, a recent fracture of a rib was the primary reason for hospitalization. The carcinoma of the tibia had already progressed so far that a pathological fracture occurred two weeks after her admission to the hospital.

The correct diagnosis was obvious in the first case because of the far-advanced osteolytic process. The second case was somewhat complicated because of a typical osteomyelitis. The roentgen findings, however, were similar to those reported by Hellner, and therefore the diagnosis of a malignant condition could be established without undue delay.

REVIEW OF THE LITERATURE

Ulcer carcinoma was first described in 1828 by Marjolin. A few years later, in 1835, Hawkins reported 7 cases, one of which represents a distinct fistula carcinoma secondary to chronic osteomyelitis. At that time, he considered the new growth as being malignant in the very lowest degree and called it a warty tumor rather than a carcinoma. Six years later, however, he revised his opinion and realized the true cancerous nature of the growth.

According to all authors who have reported on this subject, the tibia is the bone most often invaded; only in cases of fistula carcinoma have the femur and the foot sometimes been the site of the lesion. Devars, in 1894, collected 39 cases from the literature and found the following frequency of involvement: tibia, 26 cases; femur, 5 cases; foot, 5 cases; arm, 2 cases; knee, 1 case.

Benedict, who in 1931 reported the largest single group of 12 fistula carcinomas from the Massachusetts General Hospital, found involvement of the tibia 8 times, of the foot 3 times, and of the femur only once.

Ulcer carcinoma affects females three times as frequently as males according to Volkmann (1889). Fistula carcinoma, however, is predominantly observed in males.

The literature on the subject has been scanty in the three decades prior to 1930 and the disease seems to have occurred more commonly in the last century for several reasons:

(1) Precautions, as well as proper care of industrial accidents, were not as well organized as nowadays.

(2) The skin of the leg was often damaged in childhood by the punishing whip; the inflicted wounds healed slowly, and the resulting scars were tender and broke open easily.

These deductions are made from the study of numerous case records and are corroborated by the fact that ulcer carcinoma, such as described in Case 1, has become extremely rare in the last few decades.

Ulcer carcinoma occurs most frequently in women following a history of varicose veins and recurrent ulcers for thirty to forty years. In addition to the ulcers, Volkmann cites the following underlying conditions: (1) callus and scar tissue, (2) nevus and congenital wart, and (3) acquired wart.

Fistula carcinoma is observed most frequently in men of advanced age. The average duration of the underlying osteomyelitis is also thirty to forty years, the shortest interval being nine years (Case 11 and cases of Krey and Vernengo). The youngest patient, reported by Rehn, developed osteomyelitis at twelve, and fistula carcinoma at twenty-nine years of age. Vernengo's patient was thirteen years old at the onset and only twenty-two when the diagnosis of cancer was made. In the first case of Collins, though osteomyelitis had set in at the age of four years, it was thirty-nine years before malignant degeneration took place. The oldest patient, seen by Volkmann, had fistulae for sixty-six years and finally developed a carcinoma at the age of seventy-six.

From the standpoint of pathogenesis, Brunschwig and Milgram emphasized the significance of epithelization of osseous sinuses and chronic fistulae which has been known to pathologists (Kaufmann), especially in tuberculous lesions (Erdheim). A new feature was the presence of pearl formations, which Brunschwig observed in 3 cases and which he considered a precancerous condition.

There is a wide variation in the incidence of fistula carcinoma as reported by different authors. In a series of 2,400 cases of osteomyelitis, Benedict lists 12 (0.5 per cent) instances of fistula carcinoma; 5 (or 0.2 per cent) were observed by Henderson and Swart in a series of 2,396 cases; and in a small series of only 43 cases of osteomyelitis, Collins reports 2 (4.6 per cent) of fistula carcinoma.

Carcinoma develops less frequently in tuberculous bone lesions than in common osteomyelitis (Hellner). A syphilitic condition as the underlying disorder has been described by Esmarch. Cases with original compound fractures were seen by Borchers, Rehn, and others.

Metastatic involvement of lymph glands is rare. In many cases, however, there is inflammatory enlargement of the regional nodes. Metastatic lesions in the skeleton, the liver, kidney, and other viscera were found in only 6 authentic cases (Bereston and Ney). A case with metastatic lesions in the skin was recently reported by Stewart, Obermayer and Woolhandler.

DISCUSSION

Diagnosis. Clinically, the development of malignant degeneration is characterized by a fairly sudden onset, with loss of weight and strength, and with secondary anemia. Chronic ulcers and fistulous openings begin to spread and to secrete foul-smelling pus; the edges of the wound become indurated, elevated and folded like cuffs. As the tumor progresses, irregular papillary and wart-like granulations develop in the center, and finally a cauliflower growth denotes carcinoma. In fistula carcinoma the tumor forms at or near the skin. However, a few cases have been observed in which the carcinoma originated within a deep-seated osseous sinus. In these rare instances, the malignant condition may be suggested by pain and hemorrhage with rather sudden increase in secretion and foul odor.

Roentgen findings of ulcer carcinoma are characterized by a scooped-out appearance of bone, later by extensive osteolysis, and finally by pathological fracture. Osteomyelitic changes are absent in spite of an associated pyogenic process, but periosteal elevation may be noted proximal to the lesion. Roentgen diagnosis of fistula carcinoma is more difficult and, according to Benedict, is sometimes impossible when the lesion originates in a deep-seated osseous

sinus. Chronic osteomyelitis with eburnated bone and sinuses tends to mask a malignant change in the beginning, but later in the disease there is decalcification, rapidly progressing rarefaction and surface erosion of bone, and finally a pathological fracture.

Biopsy is always advisable in order to verify the presence of a carcinoma prior to radical operations. One must keep in mind, however, that it may be difficult to obtain a proper specimen when the neoplasm develops in a deep-seated sinus.

Fig. 4. Epidermoid growth, without suppuration, invading the distal phalanx of the great toe. The erosion is irregular and fringe-like and not as smooth as in ulcer carcinoma.

Differential Diagnosis. The presence of associated soft tissue involvement distinguishes ulcer carcinoma from metastatic lesions and from rare primary neoplasms of bone. In contrast to the smooth osseous defect in ulcer carcinoma, an irregular erosion of bone with a fringe-like border may be found in non-ulcerating epidermoid tumors. This difference was shown in the following rare case previously reported from a pathological standpoint by Levine and Lisa: No. 50147, F. H., white male, aged sixty-five, admitted in 1936 with a hornifying squamous cell growth of a great toe. The neoplasm eroded the underlying bone in an irregular fashion. There was localized decalcification, but no evidence of osteomyelitis or of other bone reactions (Fig. 4).

Fistula carcinoma must be differentiated from sarcoma. In a peculiar case, reported by Henderson and Swart, sarcomatous degeneration of a chronic osteomyelitis was diagnosed histopathologically. Later, a regional lymph gland was found to contain typical squamous carcinoma. Sarcoma has been repeatedly noted following roentgen therapy of tuberculous osteomyelitis (Baumann, Beck, Hanke and Neuhaus, Jaruslawsky and Marsch). Marked periostitis secondary to varicose ulcers may simulate osteomyelitis, and when rarefaction of bone is present at the same time, a neoplastic invasion may be suspected. The following case is cited to illustrate the difficulties of a differential diagnosis in such cases.

Fig. 5. Marked periostitis of the bones of both legs secondary to varicosities of thirty-six years' standing. No evidence of osteomyelitis or osteolytic process. Streaks in mid-shaft of left tibia in the vicinity of chronic skin lesions arouse suspicion of destructive bone changes, but are due to osteoporosis on an arteriosclerotic basis.

E. L., white female, aged seventy-two, was admitted in November, 1941, with a history of varicose ulcers for thirty-six years. Recently, a chronic ulcer had begun to spread around the leg in the form of superficial granulations. Roentgen study revealed advanced periostitis of tibiae and fibulae, marked calcification of arteries, and calcified thrombi in the popliteal spaces and elsewhere. Peculiar streak-like areas of lessened density were noted in the mid-shaft of the tibia close to the granulation tissue (Fig. 5). These changes aroused the suspicion of malignant invasion. However, since the findings remained stationary for six months, they were believed to be due to osteoporosis on an arteriosclerotic basis.

Prognosis. A fatal outcome is usually the result of surgical shock, secondary anemia, kidney and liver damage, and septicemia. It is rarely due to metastatic lesions. In spite of the advanced age of most patients, there have been numerous five year survivals, and Volkmann reported a case in which the patient survived for twenty-five years.

Therapy. When the malignant involvement is recognized early, a localized excision or resection may result in permanent cure (Collins); but since the disease tends to progress rapidly, amputation and even regional lymphadenectomy are necessary in most cases. The operative mortality has been greatly reduced by refrigeration anesthesia as developed especially for old people by Crossman and his coworkers. Postoperative radium and roentgen treatment of the stump and of the lymph glands has been recommended by Henderson and Swart, but preoperative irradiation is contraindicated because of the danger of sarcomatous degeneration.

When there is epithelization of osseous sinuses without evidence of carcinoma, Brunschwig considers the advisability of amputation because of a potentially malignant lesion. Two objections may be made to this radical prophylactic procedure: (*a*) while epithelization of old sinuses and fistulae is frequent, especially in tuberculous lesions, fistula carcinoma is rare, particularly in tuberculosis; (*b*) even in case of malignant degeneration there is ample time for amputation, since distant metastatic lesions are exceedingly rare.

SUMMARY AND CONCLUSIONS

(1) Direct invasion of bone by epidermoid carcinoma is rare and occurs mostly in the tibia due to its proximity to the skin.

(2) The predisposing ulcers of the leg and draining osseous sinuses may exist for many years and even decades and a malignant degeneration may therefore be overlooked.

(3) Cases of an ulcer carcinoma and a fistula carcinoma are reported. The characteristic clinical and roentgenologic features and the differential diagnosis are discussed.

(4) The prognosis is favorable, even in advanced cases, since distant metastatic lesions have been observed on only six occasions.

(5) Amputation of the diseased leg is usually indicated, unless an early diagnosis allows more conservative procedures.

(6) In chronic osteomyelitis, efforts should be made to cure residual active foci. With an increase in secretions and development of pain and hemorrhage, periodic roentgenologic and biopsy studies are advisable to determine the presence of an epidermoid carcinoma.

Addendum: Since the manuscript was submitted, an interesting article on "Adamantinoma of the tibia" by Dockerty and Meyerding* has appeared. The authors reported 2 cases from the Mayo Clinic in addition to 14 cases previously recorded in the literature and concluded from a histopathologic standpoint that tibial adamantinomas are merely modified squamous cells which vary considerably in their differentiation into ameloblasts.

The fact that the adamantinoma is closely related to the epidermoid carcinoma finds further corroboration in the following common chracteristics:

(1) Long history of chronic irritation with episodes of either initial or aggravating trauma.

(2) Sites of predilection in the tibia, jaw bones and skull.

* Dockerty, M. B., and Meyerding, H. W. Adamantinoma of the tibia; report of 2 new cases. *J. Am. M. Ass.*, 1942, *119*, 932–937.

(3) Development in a bone cyst or osseous sinus.

(4) Tendency to remain localized and absence of distant metastases in most cases.

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Vol. 50, No. 5

FRACTURES OF THE RIB CAGE FOLLOWING INTERSTITIAL RADIUM THERAPY FOR CANCER OF THE BREAST

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THE effect of roentgen and gamma radiation upon bone is not well understood. In 1903 Perthes[11] called attention to the influence of roentgen rays and radium on the epiphyseal growth of long bones. Recamier and Tribondeau[14] in 1905 demonstrated experimentally that bone growth could be retarded by a roentgen-ray dose so small that it caused no change in the bone cells. In 1910 Cluzet[2] demonstrated that irradiation inhibits or delays callus formation after a fracture. In 1922 Regaud[15] called attention to bone necrosis following roentgen and gamma irradiation. The conclusions reached by Ewing[5] in 1926 from a study of 3 cases of bone necrosis after heavy irradiation for bone tumor are significant. He states that (1) moderate irradiation greatly reduces the growth capacity of bone cells, and the bones are united after fracture by the formation of an unusually hard callus; (2) after more severe irradiation, such as that which falls within the upper limits of therapeutic measures now commonly employed, there may be established a progressive productive osteitis which may cause marked thickening of the shafts, mostly at the expense of the marrow cavity, and in the case of cancellous bone may largely replace the fat and cellular marrow by poorly formed and brittle bone or calcified osteoid tissue; (3) severe therapeutic irradiation of bone produces a peculiar change in the structure and composition of lamellar bone which is shown in increased fragility and a marked tendency to spontaneous fracture. Under favorable conditions, however, the fractures may slowly heal. After such irradiation the bone is nearly devoid of circulation, and the periosteal vessels are generally much sclerosed; (4) heavy irradiation renders the shaft of a bone very brittle and prone to spontaneous fracture; the periosteum is injured and a persistent mass of indolent tissue prevents the restoration of function of the limb. In 1934 Colwell and Russ[3] wrote: "Adult bone is relatively resistant to x-ray and injuries from this cause are rare."

A full appreciation of this irradiation effect can be had only by an understanding of the anatomy and physiology of the structures involved.

ANATOMY

The ribs (Gray[6]) are elastic arches of bone which form a large part of the thoracic cage. On the inferior border of the shaft is a groove for the intercostal vessels and nerve. Within the groove are seen numerous small foramina for nutrient vessels which traverse the shaft obliquely from before backward. The blood supply of the ribs is derived from the internal mammary artery which supplies the anterior intercostal branches, and from the thoracic aorta with the exception of the two superior intercostal spaces, which are supplied from a branch of the subclavian.

PHYSIOLOGY

The physiology of bone (Boyd[1]) is a little less familiar than the anatomy. It is the great calcium and phosphorus reserve of the body, a reserve which is continually being drawn upon or added to, so that its structure is not fixed and permanent. It is composed of living cells and a hyaline matrix impregnated with calcium salts. The vital character of bone is illustrated by the words of Sir Charles Bell, written more than a hundred years ago: "Scrape a bone

* Presented at the Twenty-seventh Annual Meeting, American Radium Society, Atlantic City, N. J., June 8–9, 1942.

and its vessels bleed; cut or bore a bone and its granulations sprout up; break a bone and it will heal; burn it and it dies."

All bone (Piersol[13]) wherever found is formed through the activities of specialized connective tissue cells, the osteoblasts. The methods of bone formation are: (1) direct or intramembranous, (2) endochrondral, (3) periosteal. The ribs develop by the intramembranous and periosteal methods whereby the bone matrix is formed by the osteoblasts directly within the layer of young connective tissue.

Knowledge of changes in bone resulting from interruption of circulation has made slow progress. Phemister[12] offers a number of reasons for this: (1) the absence or mildness of immediate symptoms from simple interruption of circulation; (2) postmortem studies of the skeleton are less common and less extensive than those of the viscera; (3) operation offering a chance for pathologic examination is seldom indicated with most forms of aseptic necrosis; (4) the roentgen signs of the condition, which are late in appearing, were long confused with those of other chronic lesions.

There are two chief factors in the absorption of bone, one related to the vascular supply and the other to the bone-forming cells. Persistent vascular dilatation is followed by widening of the canals at the expense of bone, and as the absorption becomes marked the condition of rarefaction or osteoporosis occurs. It would appear that in primary vascular resorption the mechanism by which calcium is removed and the canals widened is a physicochemical one. Any excessive local production of carbon dioxide tends to cause solution of calcium, for the solubility is directly affected by the carbon dioxide tension of the blood and tissue fluid. For these reasons only well vascularized living bone can be absorbed quickly. Dead bone is absorbed slowly by osteoclasts (Boyd[1]).

There are two requisites for ossification: (1) an adequate blood supply, and (2) an adequate supply of calcium. Emphasis is placed upon the importance of circulatory disturbance in modifying the structure of bone. Hyperemia is followed by decalcification and osteoporosis, lessened circulation, and loss of blood supply by necrosis. Repair of bone is carried out entirely by the osteoblasts which line the deep layer of the periosteum, the endosteum and the haversian canals. The essential function of the periosteum is to supply the outer part of the bone with blood. Removal or separation of the periosteum is apt to be followed by death of this part of the bone (Boyd).[1]

More recently the literature has contained reports of injuries to bone, especially the neck of the femur in patients treated for cancer of the cervix uteri, as described in 1936 by Dalby, Jacox and Miller.[4] In a more recent report, Paul and Pohle[10] have described irradiation osteitis following postoperative prophylactic irradiation for cancer of the breast.

In 1933 and 1934, when our first patients with cancer of the breast were treated by interstitial irradiation, it was thought that adult bone was so radioresistant that the therapeutic dose employed would have no deleterious effect upon the ribs. Since that time our experience has demonstrated that bone is not so radioresistant as was formerly thought and that permanent damage can result from a therapeutic dose applied to a nearby neoplasm. We have been unable to find any report of rib fractures attributable to gamma radiation. Pack[9] states that he has seen rib fractures following interstitial radiation therapy of mammary cancer.

We wish to present a group of 10 patients (Table 1) who have developed fractures of the ribs following treatment by interstitial radium element needles for cancer of the breast. These patients have remained free of clinical evidence of cancer for periods ranging from four to nine years.

METHOD USED IN INTERSTITIAL IRRADIATION

This method of treatment was first used in this country by Lee[8] at the Memorial Hospital, but he used radium emanation by interstitially placed platinum needles for primary breast cancer. In 1922, Keynes[7] of

TABLE I
SUMMARY OF TEN CASES

Name Case No.	Age	Date and Dosage of Preradium Roentgen Radiation	Date and Dosage in mg-hr. Radium	Surgery	Symptom	Date Fracture First Observed	Time from Treatment to Fracture	Remarks Living and Well (free of cancer)
B. P. 2381	61	0	2-13-33 24,240 6-23-36 13,370	Excision tumor	Catchy pain	10-14-38	5½ yr.	9 yr.
F. S. 2379	40	0	6-19-33 21,120	Excision tumor	None	6-29-40	7 yr.	9 yr.
A. A. 2408	57	0	7-17-33 26,164	Biopsy	None	11-1-40	7 yr.	9 yr.
J. O. 5313	48	9-27-37 2080 r	4-17-37 12,116 1-12-38 7511	Biopsy	None	6-11-41	4 yr.	Died of embolus; no evidence of cancer at autopsy
J. McG. 5279	70	10-10-37 1800 r	12-6-37 18,866	Biopsy	None	10-18-38	2 yr.	4½ yr.
R. B.* 5503	21	0	2-8-38 15,573 3-24-38 2895	Biopsy	None	8-26-39 2-29-40	18 mo.	4 yr.
J. S. 5542	57	0	3-30-38 31,941	Biopsy	None	5-17-40	2 yr.	4 yr.
E. F. 5723	42	0	6-21-38 26,051	Tumor excised	None	11-13-39	18 mo.	4 yr.
C. B. 5786	49	0	7-28-38 25,080	Tumor excised	Pain	6-5-39	11 mo.	4 yr.
J. M. 1511		0	8-9-38 23,723	Simple mastectomy	Soreness in axilla	10-4-39	14 mo.	4 yr.

* Sarcoma of pectoral muscle.
r, number of roentgens to each of three fields (measured in air).

London began to treat recurrent breast cancer with interstitially placed radium element tubes. There finally developed a systematic method of implantation of the entire breast, axilla and supraclavicular area (Fig. 1). This method, as outlined by Teahan,[16] consists of the application of two types of platinum needles with a wall thickness of 0.8 mm. One type is 44 mm. long and contains 2 mg. of radium; the other is 60 mm. long and contains 3 mg. of radium. The linear intensity of the active length is the same for the two types of needles. The size and position of the tumor and the size of the breast are taken into consideration in planning the implantation. The irradiated area extends from the sternum to the posterior axillary line, and from the supraclavicular fossa to the costal margin. The primary tumor and surrounding breast are first implanted. The longer needles are used for this and are placed in

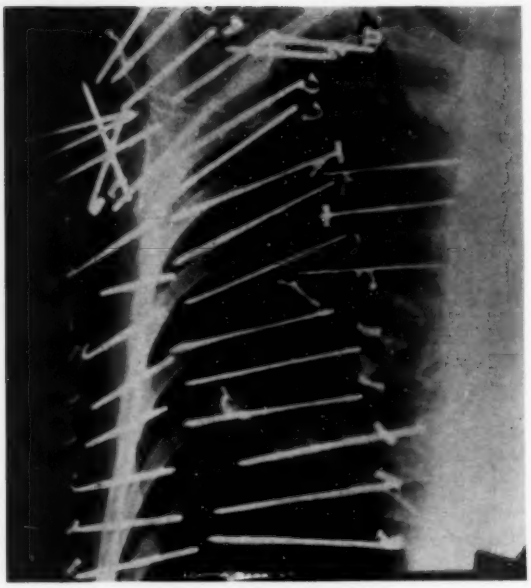

FIG. 1. Roentgenogram showing the location of the radium needles in a typical case.

such a manner that they lie parallel to each other and 1.5 cm. apart on a plane just beneath the tumor, either just above or just below the fascia. Two rows are generally used, the ends of the needles overlapping slightly. In a very thick breast, a row is also placed superficial to the tumor. Two of the 2 mg. needles are placed side by side below the center of the clavicle and 1.5 cm. apart, their points directed toward the axilla. Two 2 mg. needles are placed at the base of the neck above the clavicle and parallel to it. One 2 mg. needle is placed in each of the four upper intercostal spaces in such a manner that the point of the needle lies against the posterior lateral edge of the sternum. The number of needles used depends upon the area to be irradiated. Many factors, such as the size of the breast, the size of the tumor, and the extent of involvement, must be considered in determining the amount of radium to be used and the length of time it is to remain in place. The radium is usually left in place for 160 to 240 hours. The average amount of radiation delivered is 22,000 milligram-hours.

Two of the cases reported here received roentgen therapy prior to the application of interstitial radium. In both cases the treatment amounted to 1,800 to 2,000 r, measured in air, to each of three fields. In 1 case a simple mastectomy was performed at the time of radium implantation. In 4 cases the tumor was excised, and in 5 cases a biopsy specimen was taken from the tumor.

CLINICAL COURSE

The first reaction is a mild erythema about each perforation, which occurs about the seventh day. The erythema becomes generalized by about the tenth day, and the height of the reaction is reached on about the eighteenth day. Complete healing takes place in four to six weeks. Bronzing persists for eighteen to twenty-four months. Regression of the tumor is first noted about two weeks after completion of the treatment. In most cases the tumor will have disappeared in six months. Scarring of the breast occurs with fixation of the deformed breast and underlying soft tissues to the chest wall. The persistent induration makes it difficult to differentiate between residual disease and the fibrosis resulting from irradiation.

All cases are followed in the out-patient clinic at intervals not greater than three months, as far as this is possible. Nearly all patients complained of soreness of the breast area immediately following treatment. In most instances this soreness subsided within the first year.

Fractures of the ribs were noted on the chest roentgenograms which are made at intervals for detection of pulmonary metastasis. Some patients volunteered no symptoms referable to the rib cage. In these cases careful questioning after roentgenographic discovery of rib fracture revealed no instance of trauma. A few of the patients mentioned "soreness" or "catchy pain," but in no instance were the symptoms disabling or distressing.

These fractures were at first attributed to neoplastic invasion. It was soon found however, that the rib changes were confined to the area treated (there being no roentgenographic evidence of similar changes elsewhere in the skeletal system),

and that a diagnosis of skeletal metastasis was at variance with the patient's excellent condition as noted on clinical examination. All the available cases of mammary cancer which had been treated by interstitial irradiation were returned for roentgen studies of the ribs, and fractures were found in 21 of these patients.

DIAGNOSIS

A complete skeletal survey (roentgenographic) is made prior to the institution of treatment for mammary cancer. The earliest change detected was a simple fracture of the rib eleven months after treatment

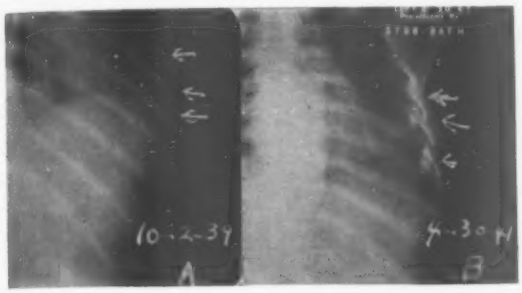

Fig. 2. C. B. (No. 5786). *A*, October 2, 1939. Four months after discovery of the fracture with early demineralization and minimal sclerosis. *B*, April 30, 1941. Further demineralization with separation of fragments of multiple fractures of the ribs.

(Fig. 2). In this patient the texture of the bone and the mineral content adjacent to the fracture were normal. Subsequent changes noted were increased density of the bone adjacent to the fracture line (sclerosis) and absorption of the ends of the fragments so that the separation of the fragments became more marked. In most instances the fractures were first detected from fifteen to eighteen months after treatment (Fig. 3). These showed a separation of the fragments of from 3 to 10 mm., with some demineralization of the bone adjacent to the fracture for 2 to 5 mm. and then sclerosis of the bone beyond the area of demineralization, for a distance of 3 to 5 cm. (Fig. 4). The process was so slow that the appearance remained much the same for many months. Later, fragmented callus developed about the fragments, but union did not occur (Fig. 5). In some of the oldest

Fig. 3. J. McG. (No. 5279). *A*, October 18, 1939. Fracture discovered two years after radiation treatment. There is bone absorption. *B*, September 27, 1940. One year later. The changes are slow with more bone absorption and separation of the fractured ends of the ribs.

cases large fragmented masses of callus are visualized about the site of non-union. In some of the older cases the rib fragments are separated as much as 3 cm., and in these the ends of the bones are smooth and pointed and devoid of callus (Fig. 6).

The number of ribs fractured varied from one to five, with most cases showing three or four ribs involved. All the fractures occurred between the mid-clavicular and mid-axillary lines, and usually the third to sixth rib was involved.

It must be kept in mind that the ribs in this area received the largest amount of radiation, as the overlying structures are not thick here as elsewhere.

PATHOLOGIC FINDINGS

In postmortem material from one case, a roentgenogram of the gross specimen re-

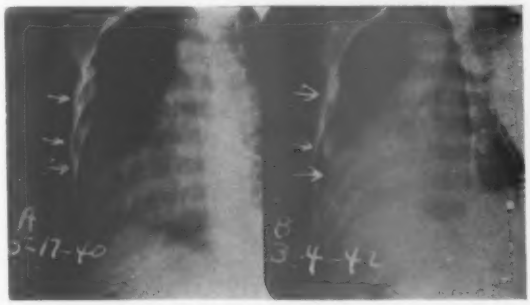

Fig. 4. J. M. (No. 1511). *A*, May 17, 1940. Multiple ribs involved with separation of fragments and moderate demineralization. *B*, March 4, 1942. Wider separation of the fragments with increased sclerosis.

FIG. 5. J. M. (No. 1511). Body section roentgenogram with three ribs involved and fragmented callus about the ends of the fracture.

veals sclerosis of the bone together with areas of demineralization (Fig. 7). The fragment of bone adjacent to the fracture is pointed and smoothed off.* Microscopic examination reveals the following (Fig. 8): The bone is normal in general structure and has a compact layer on the surface enclosing the spongy central tissue. The haversian systems, however, appear disturbed, and in many of the canals the blood vessels seem degenerated. The ground-substance of the bone itself contains basophilic lines

* Postmortem and microscope examinations were made by Dr. W. S. Hastings, pathologist, Jeanes Hospital.

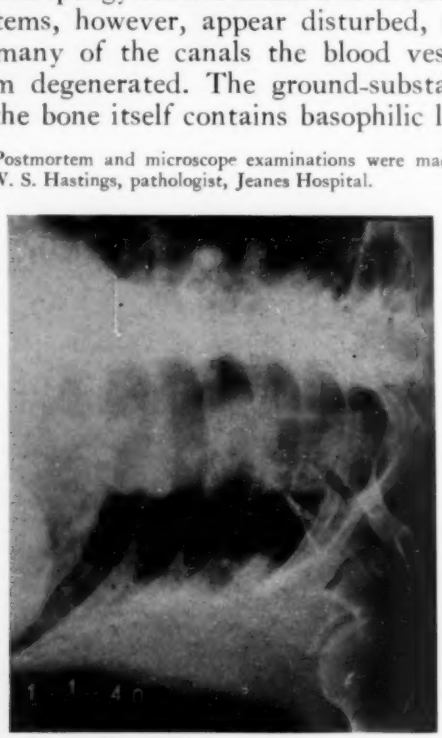

FIG. 6. A. A. (No. 2408). November 1, 1941. Seven years after treatment, showing marked deformity of multiple ribs and fragmented callus.

FIG. 7. J. O. (No. 5313). Portion of fractured rib removed at necropsy. End of fracture is smooth. There is moderate sclerosis and demineralization.

and streaks of uncertain significance. The bone cells in the lacunae are granular and in many no nuclei can be recognized. The fat tissue in the spongy bone is fairly regular, but blood vessels are few in number and those found are hyaline. There is no hematopoietic tissue. The picture is one of partial necrosis, due possibly to some physical agent. No tumor of any kind is found.

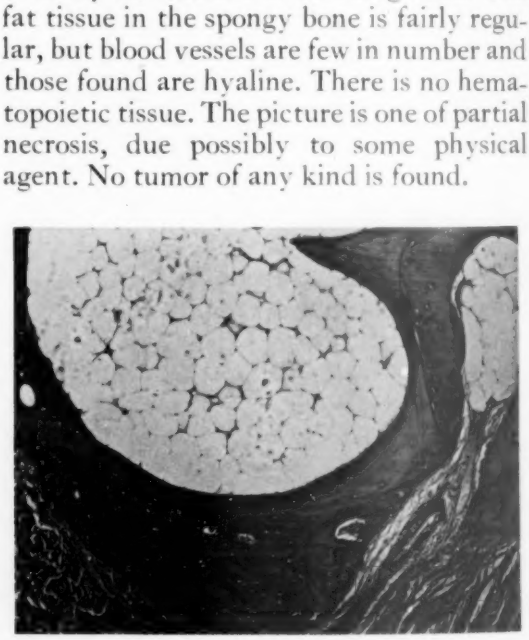

FIG. 8. J. O. (No. 5313). Same case as shown in Figure 7. No evidence of metastasis. Degeneration of blood vessels. They are few in number and those found are hyaline.

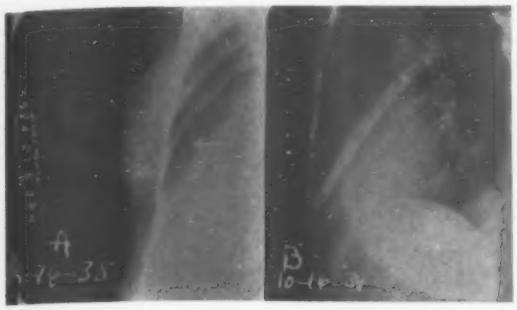

Fig. 9. L. L. (No. 5524). *A*, February 16, 1938. Rib destroyed by cancer prior to radium therapy. *B*, October 16, 1939. Eighteen months after treatment by radium showing complete degeneration of the rib.

SUMMARY AND CONCLUSIONS

We have presented ten patients who were treated with gamma radiation for cancer of the breast and who subsequently developed fractures of the ribs. These patients are free of clinical evidence of local or metastatic disease. In most instances the fractures appeared in less than two years. In our early experience we were not in the habit of making roentgenograms of the chest in the absence of symptoms, and consequently many fractures were doubtless present long before their discovery. In one case a fracture was detected as early as eleven months after treatment.

In the differential diagnosis traumatic fracture and neoplastic invasion must be considered. We believe that a traumatic fracture can be ruled out on the basis of a careful history in each instance. In neoplastic invasion the area treated shows regeneration of bone (Fig. 9). The lack of progression of destruction and the smoothing off of the ends of the fragments militates against a neoplastic process. Despite histopathologic verification, except in one case, we believe that the clinical condition of the patient and the lack of evidence of cancer elsewhere justifies the consideration of these rib changes as due to a non-neoplastic post-gamma irradiation effect. We believe that this effect is brought about by an interference with the blood supply of the ribs. It is therefore evident that adult bone is not resistant to therapeutic irradiation directed to a nearby neoplasm.*

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* For discussion see page 627.

SOME OF THE EFFECTS OF ROENTGEN IRRADIATION ON THE CARDIOVASCULAR SYSTEM*

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THIS report concerns itself with the different effects that may be produced in the heart and circulation by high voltage roentgen therapy when it is used in treating cancer in different regions of the body. We have attempted to approach the problem with an open mind. One should not conclude that circulatory disturbances occurring during or after the time that radiation is given are necessarily the result of roentgen rays. One must realize that such disturbances may be the result of other factors secondary to the malignant disease itself instead of the therapeutic agent used.

From 1895 to 1932, there were numerous reports[4,6,8,9,10,18,20,21,22] in the literature by many different investigators on the direct and indirect effect that roentgen therapy had on the heart and circulation. These included both clinical and animal studies. While the majority of findings favored the conclusion that there was no appreciable effect on the heart, some excellent observers concluded that both early and late cardiac damage might accrue from high voltage roentgen rays.

In 1932 Desjardins[5] reviewed all the work done up to that time and, after a careful analysis of the results in the light of his experience, concluded that while the heart could be damaged by excessive doses of roentgen radiation, there was probably no danger of cardiac injury from radiation as it was used at that time. From 1932 to 1941 there were no further reports in the literature.

It seemed to us at the Memorial Hospital that instances of cardiac disease such as arrhythmias, myocardial failure and symptoms suggesting circulatory insufficiency did occasionally occur during and after a course of roentgen therapy. While we had no evidence that these were the result of the treatment, at least there was no direct evidence that they were not.

ANIMAL EXPERIMENT

In order to check the results of other workers and to determine the dose at which myocardial change is evident following high voltage roentgen therapy, we undertook some animal experiments on adult rats.

In the first group of animals,[15] the immediate effects on the hearts were determined. Animals given single doses ranging from 750 to 20,000 r through a small precordial portal were sacrificed at weekly intervals.

From these experiments, it was found that at least 10,000 r delivered in a single dose was necessary to produce microscopic evidence of myocardial damage. These changes consisted of degeneration of the muscle fibers, intermuscular edema, capillary hemorrhages and round cell infiltration. The pericardium and endocardium of the animals receiving 10,000 r were intact. The microscopic picture was evident as early as seven days after irradiation. We concluded that these changes were the direct result of the roentgen irradiation but did not constitute a specific pathological entity.

In another group of animals[16] followed for over a year and given single doses up to 7,500 r through a similar portal, no late changes such as muscular atrophy or myocardial fibrosis were found.

From both these studies one must conclude that the hearts of rats are resistant to relatively large amounts of roentgen radiation.

CLINICAL STUDY

The clinical study was started in 1938.

* From the Department of Medicine, Memorial Hospital, New York, New York. Presented at the Twenty-seventh Annual Meeting, American Radium Society, Atlantic City, N. J., June 8–9, 1942.

Our method was to examine patients before radiation therapy was started, follow them through the time therapy was given, and for many months or years after. This examination included a history, physical examination, electrocardiogram, and a roentgenoscopic or roentgenographic study of the heart and lungs. They were examined in a similar manner at the time the irradiation reaction was at its height and at intervals of three months thereafter. If the patients presented any unusual features, they were seen more frequently. Individual records were kept of each patient.

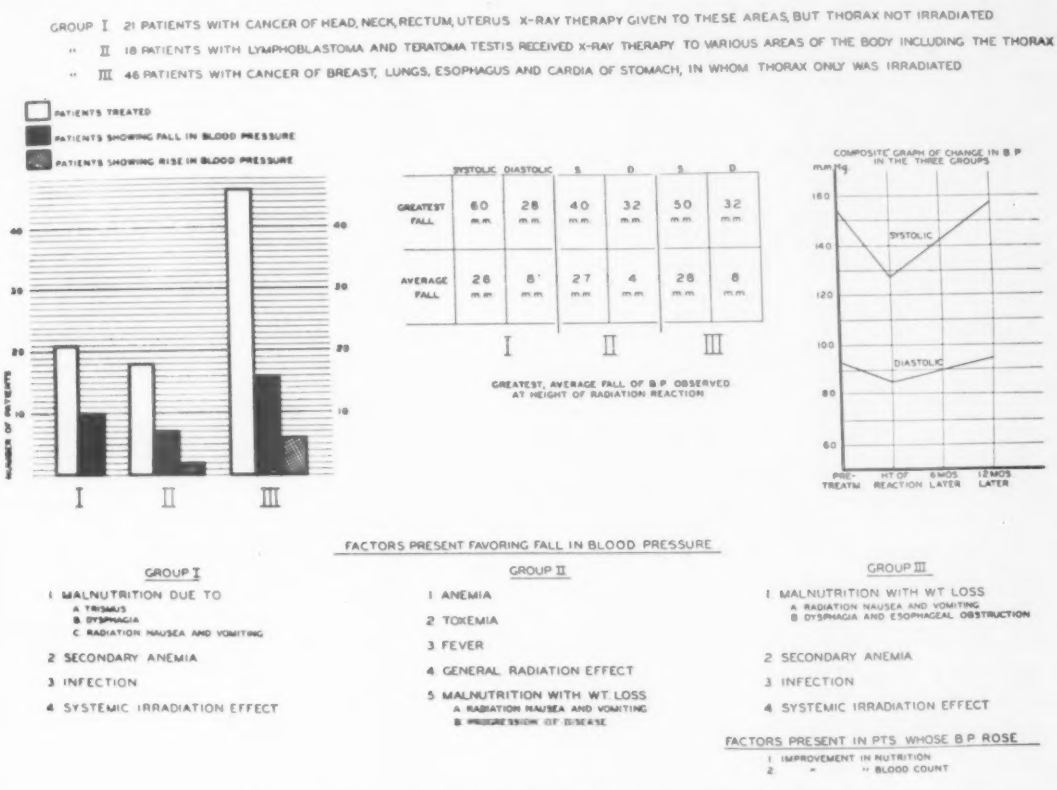
After four years, this is an analysis of the results obtained from 85 patients. They were divided into three groups for the purposes of comparison.

Group I included those with cancer of the head and neck, female genital tract, and the rectum. None of these patients had radiation therapy delivered to the thorax.

Group II included those with malignant lymphomas of various types. These patients had roentgen therapy to many regions of the body including the thorax.

Group III included those with cancer on or within the thoracic cavity. The roentgen therapy was directed solely to the thorax, and other regions of the body were not treated.

These groups included both patients with normal hearts and patients with different types of heart disease.


GROUP I 21 PATIENTS WITH CANCER OF HEAD, NECK, RECTUM, UTERUS X-RAY THERAPY GIVEN TO THESE AREAS, BUT THORAX NOT IRRADIATED
" II 18 PATIENTS WITH LYMPHOBLASTOMA AND TERATOMA TESTIS RECEIVED X-RAY THERAPY TO VARIOUS AREAS OF THE BODY INCLUDING THE THORAX
" III 46 PATIENTS WITH CANCER OF BREAST, LUNGS, ESOPHAGUS AND CARDIA OF STOMACH, IN WHOM THORAX ONLY WAS IRRADIATED
PATIENTS TREATED
PATIENTS SHOWING FALL IN BLOOD PRESSURE
PATIENTS SHOWING RISE IN BLOOD PRESSURE
NUMBER OF PATIENTS
I II III
SYSTOLIC DIASTOLIC S D S D
GREATEST FALL 60 mm. 28 mm. 40 mm. 32 mm. 50 mm. 32 mm.
AVERAGE FALL 26 mm. 8 mm. 27 mm. 4 mm. 28 mm. 8 mm.
GREATEST, AVERAGE FALL OF B.P. OBSERVED AT HEIGHT OF RADIATION REACTION
COMPOSITE GRAPH OF CHANGE IN B.P IN THE THREE GROUPS
mm Hg
SYSTOLIC
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FACTORS PRESENT FAVORING FALL IN BLOOD PRESSURE
GROUP I
1 MALNUTRITION DUE TO
A TRISMUS
B DYSPHAGIA
C RADIATION NAUSEA AND VOMITING
2 SECONDARY ANEMIA
3 INFECTION
4 SYSTEMIC IRRADIATION EFFECT
GROUP II
1 ANEMIA
2 TOXEMIA
3 FEVER
4 GENERAL RADIATION EFFECT
5 MALNUTRITION WITH WT. LOSS
A RADIATION NAUSEA AND VOMITING
B PROGRESSION OF DISEASE
GROUP III
1 MALNUTRITION WITH WT. LOSS
A RADIATION NAUSEA AND VOMITING
B DYSPHAGIA AND ESOPHAGEAL OBSTRUCTION
2 SECONDARY ANEMIA
3 INFECTION
4 SYSTEMIC IRRADIATION EFFECT
FACTORS PRESENT IN PTS. WHOSE B.P. ROSE
1 IMPROVEMENT IN NUTRITION
2 " " BLOOD COUNT
THE PRESENCE OF HYPERTENSION AND/OR HEART DISEASE DID NOT INFLUENCE THESE FINDINGS

FIG. 1.

Effect on the Blood Pressure. In general there was a drop in the blood pressure at the height of the irradiation reaction. The decrease was mostly in the systolic phase amounting to 60 mm. Hg in extreme instances but averaging about 28 mm. Hg for the three groups. The fall of the diastolic pressure was not so marked, averaging 8 mm. for all the patients.

The decrease of blood pressure following

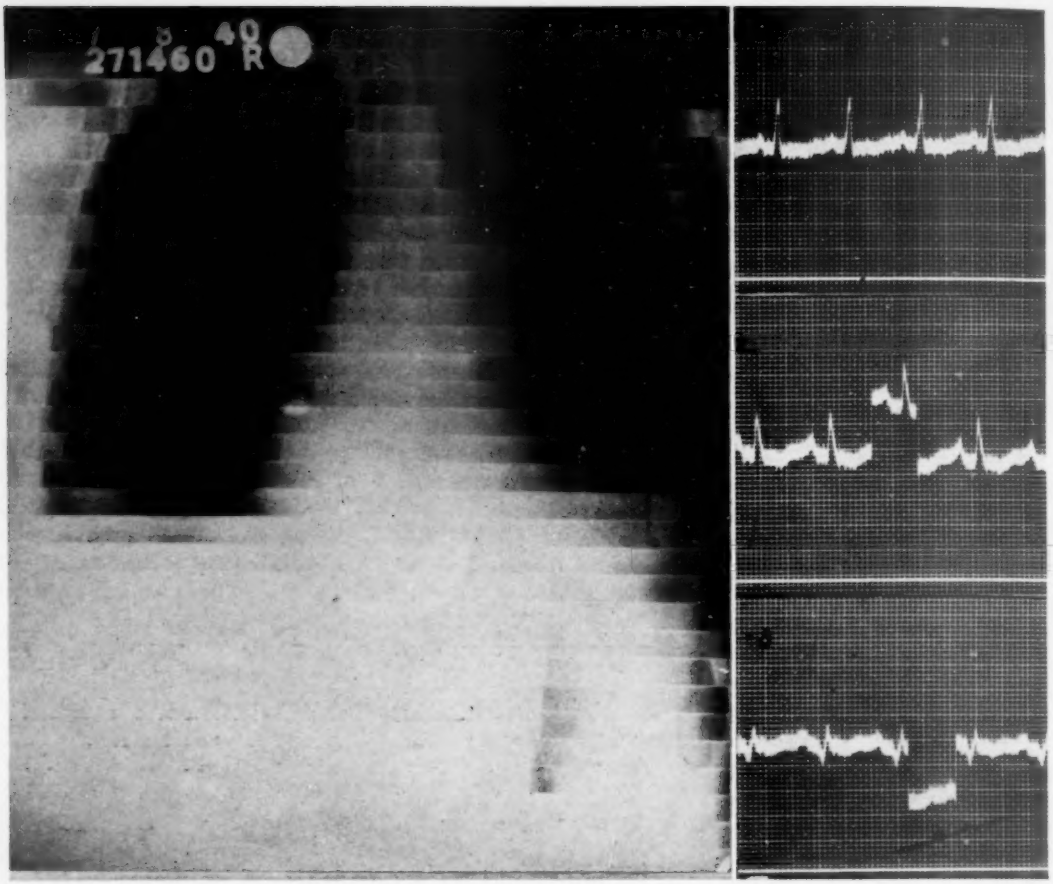


Fig. 2. Kymographic study of patient with advanced irradiation fibrosis of the lung and chronic constrictive pericarditis. Electrocardiogram shows negative T waves in all leads.

roentgen therapy has been known for many years and has been attributed both to the depressing effect of the roentgen rays themselves, and to the liberation of histamine-like chemicals into the blood with resultant vasodilatation.

From a study of the clinical records of these patients, one is forced to conclude that other factors were probably more important. Insufficient nourishment with weight loss, anemia, tumor infection, toxemia, fever and tumor cachexia were all potent factors tending to decrease the tension. Curiously enough, when patients with cancer of the esophagus are fed through a gastrostomy tube during the period they receive therapy, the blood pressure not infrequently rises. Moreover, the most marked fall in pressure occurred in patients with lesions of the head and neck, whose feeding is frequently a difficult problem because of dysphagia resulting from a pronounced irradiation reaction in the mouth or pharynx (Fig. 1).

Arrhythmias. Of the 85 patients observed, 10 showed different arrhythmias of all types ranging from the common benign ventricular premature contraction to the more severe arrhythmia of auricular fibrillation. These, with one exception, were present before roentgen therapy was instituted and followed the same course seen in patients not subjected to this type of treatment. They all responded to the usual measures used for such ectopic rhythms. However, one patient with cancer of the left lung had two attacks of paroxysmal auricular tachycardia, one during the ac-

tual treatment period and one a year later. Both attacks responded to digitalization and regular sinus rhythm was restored. A few months before death, he developed chronic auricular fibrillation without receiving any roentgen therapy. This latter rhythm may have been due to direct invasion of the left auricle by tumor. The paroxysmal tachycardia may have been of reflex origin due to hilar metastases. However, this reasoning is only speculation.

We have observed 4 patients, 3 of whom developed chronic pericarditis and 1 who developed pleuropericardial adhesions after irradiation. These patients all received a large amount of treatment to the left lung; 2 for cancer of the breast and 1 for cancer of the lung. All developed a severe degree of irradiation pleuropulmonitis with advanced changes in the skin and ribs, plus a chronically infected lung. The diagnosis of pericarditis in each was confirmed by electrocardiograms and kymographic study (Fig. 2). One patient who came to autopsy showed typical chronic adhesive pericarditis which differed in no way from that occurring in other diseases. The patient, who had pleuropericardial adhesions (Fig. 3), was treated for a mediastinal tumor of undetermined type and came under our care because of irradiation fibrosis of the lung with dyspnea as the presenting symptom. The adhesions between the pleura and pericardium, however, occurred at a lower level than the lowest margin of the portal of entry of the roentgen-ray beam.

Carotid Sinus Syndrome. Four patients were observed who developed a rather

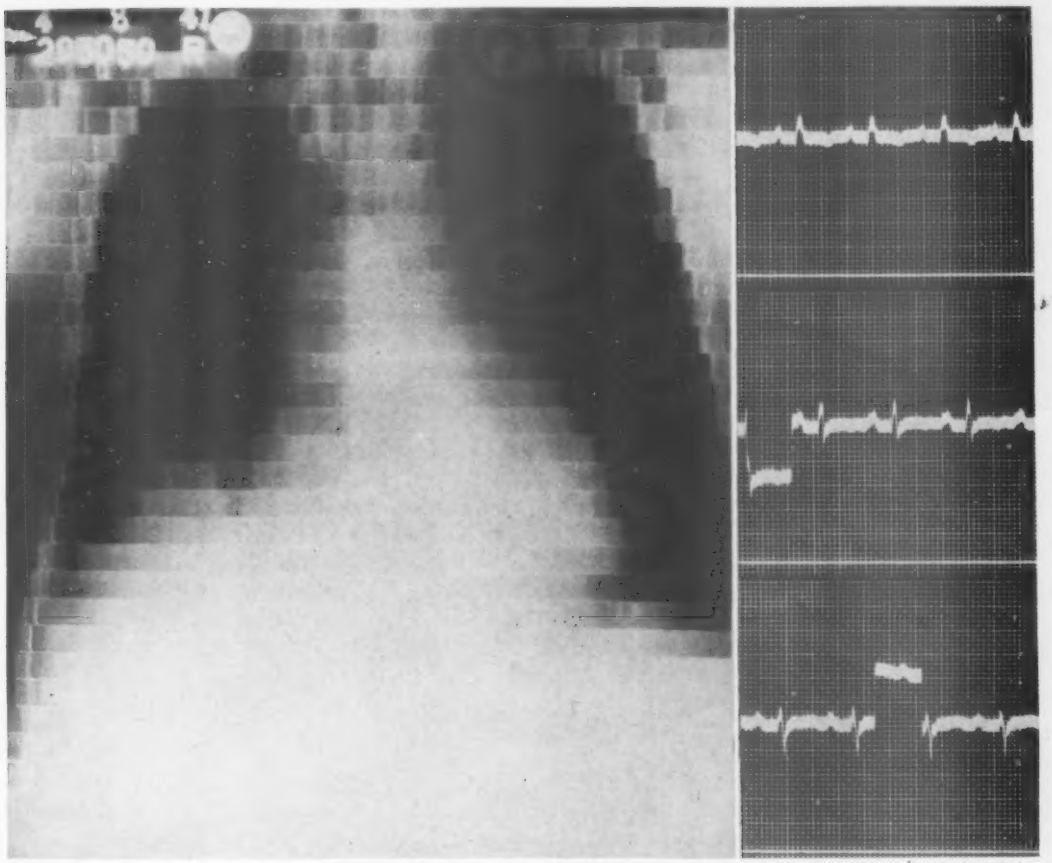


Fig. 3. Kymographic study of patient with pleuropericardial adhesions on the right side. The amplitude of the pulsations along the left cardiac border are about normal. The appearance of the electrocardiogram suggests some degree of associated pericarditis.

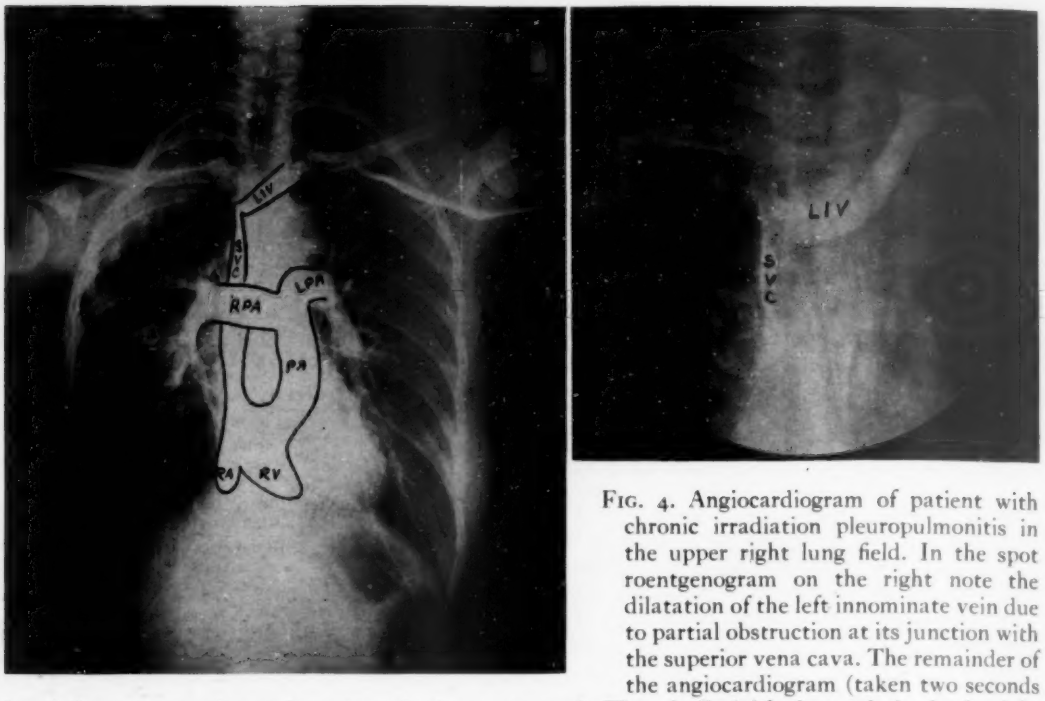


FIG. 4. Angiocardiogram of patient with chronic irradiation pleuropulmonitis in the upper right lung field. In the spot roentgenogram on the right note the dilatation of the left innominate vein due to partial obstruction at its junction with the superior vena cava. The remainder of the angiocardiogram (taken two seconds later) shows a normal vascular pattern in the great vessels. There is diminished vascularity in the right upper lung field. LIV, left innominate vein; SVC, superior vena cava; RA, right auricle; RV, right ventricle; PA, pulmonary aorta; RPA, right pulmonary artery; LPA, left pulmonary artery.

marked carotid sinus syndrome during the course of roentgen therapy. Two patients had generalized arteriosclerosis, 1 had myocardial fibrosis, and 3 had no evidence of heart disease. Three of the cases had cancer of the mouth and 1 had an extrinsic laryngeal cancer. All had inflammatory adenitis plus proved metastatic cancer in the upper cervical nodes that are intimately associated with the carotid bifurcation. The attacks were all typical in onset with syncope, lowered blood pressure, slow pulse, and 2 patients had epileptiform seizures lasting a short time. All of the patients responded promptly to the use of atropine or ephedrine sulfate. As the irradiation reaction and infection subsided the attacks ceased and did not recur.

The carotid sinus syndrome in these patients was probably due to the pressure of the infected metastatic nodes on the carotid sinus rather than any specific action of the roentgen rays.

Venous Pressure and Circulation Times. The measurement of venous pressure and the determination of circulation times are common methods used in detecting the presence of circulatory disturbances. These values have been determined on a group of patients who have had radiation directed to the heart as well as the lungs. Some had rather severe degrees of irradiation fibrosis with mediastinal displacement.

With the technique used, 6–11 cm. of water constitutes the normal range. It has been found that a considerable number of these patients have slight to moderate increase in the venous pressure. We have also noticed an increased variation of the pressure with the respiratory cycle, the pressure showing a greater fall during inspiration and a greater rise during expiration. In a group of 15 patients so studied, the pressure was above normal in about one-half of the patients.

The circulation times, both arm to lung and arm to tongue, have also been slightly increased in a few instances. None of these

patients had evidences of either right or left ventricular failure. The electrocardiograms on these patients were not those of myocardial degeneration, valvular disease or pericarditis.

A vasogram done on one of these patients has given at least one of the explanations for these unusual results (Fig. 4).

The reason for the increased venous pressure is obvious. The chemical agents used for determining the circulation times are delayed in their progress to the right heart. This would naturally give long circulation times.

In general, there were two types of alterations observed in the electrocardiograms. The first occurred in patients of all the groups and were essentially minor changes in the voltages of the different waves in serial tracings. Since these changes were present in patients both with and without heart disease, a valid reason is that they reflected the changing physiologic state of the myocardium due to anemia, infection, toxemia, weight loss due to malnutrition, tumor cachexia and possibly a depressing effect of the roentgen radiation itself. No changes in the conduction mechanism were found.

However, a more bizarre type of change

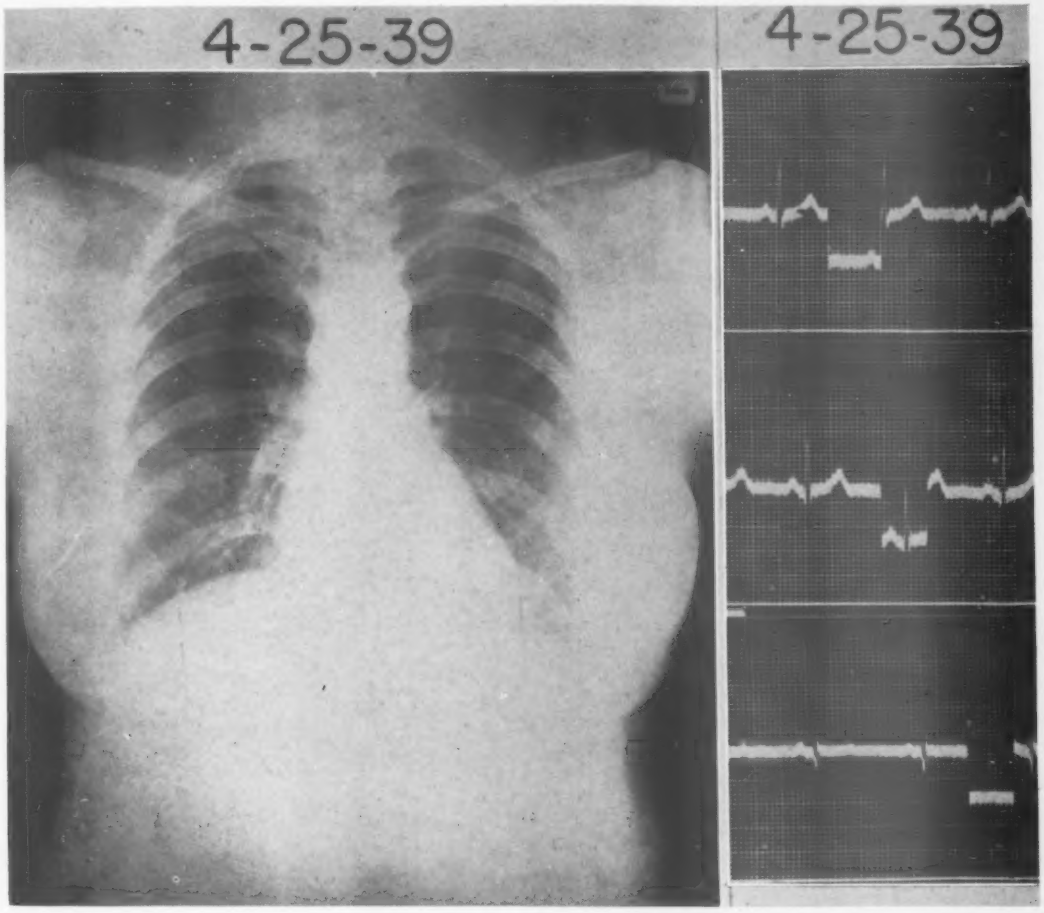
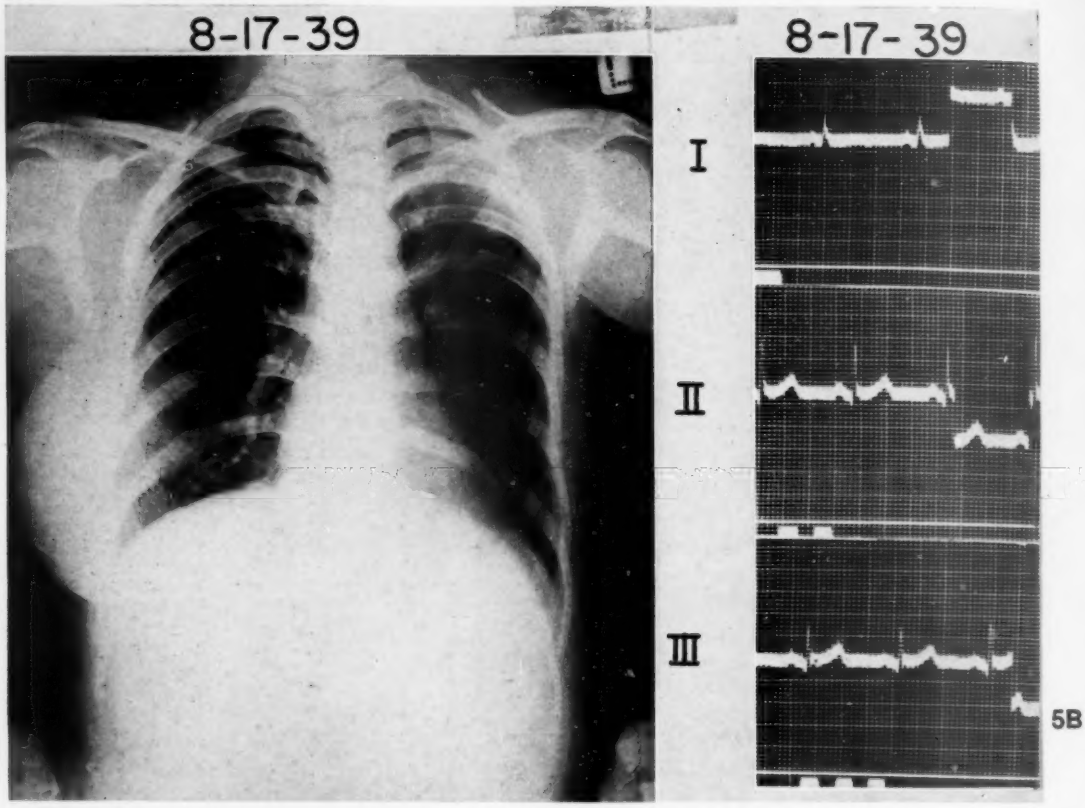


Fig. 5*A*. L. L., aged forty-three. Cancer of the left breast. *A*, before treatment; *B*, after mastectomy and roentgen therapy; *C*, twelve months after roentgen therapy; *D*, eighteen months after roentgen treatment. Note the occurrence of chronic irradiation pleuropulmonitis in the left upper lung field (*B*), and the associated changes in the electrocardiogram. T1 has become isoelectric and the voltage of T_3 has increased. The configuration of the electrocardiogram tends to return to normal after a year (*C*) but is never exactly the same as before therapy.



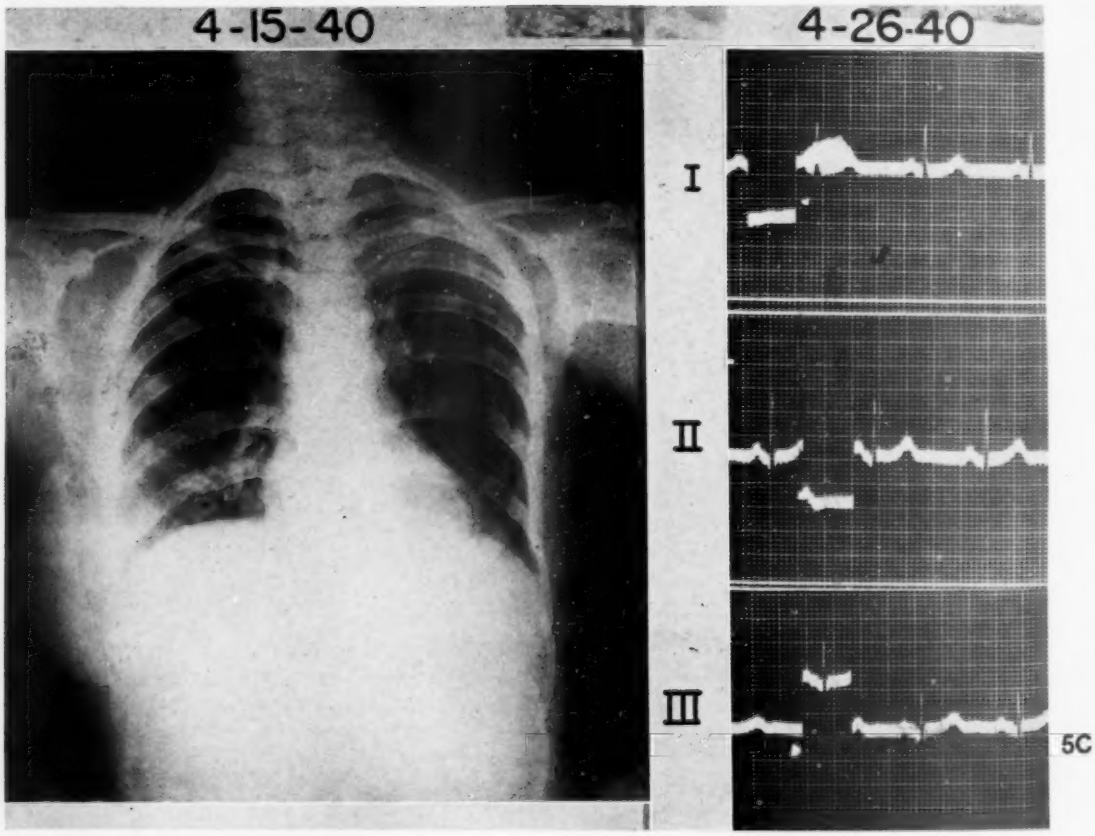


FIG. 5*B*. L. L.. aged forty-three. Cancer of the left breast. After mastectomy and roentgen therapy.

FIG. 5*C*. L. L., aged forty-three. Cancer of the left breast. Twelve months after roentgen therapy.

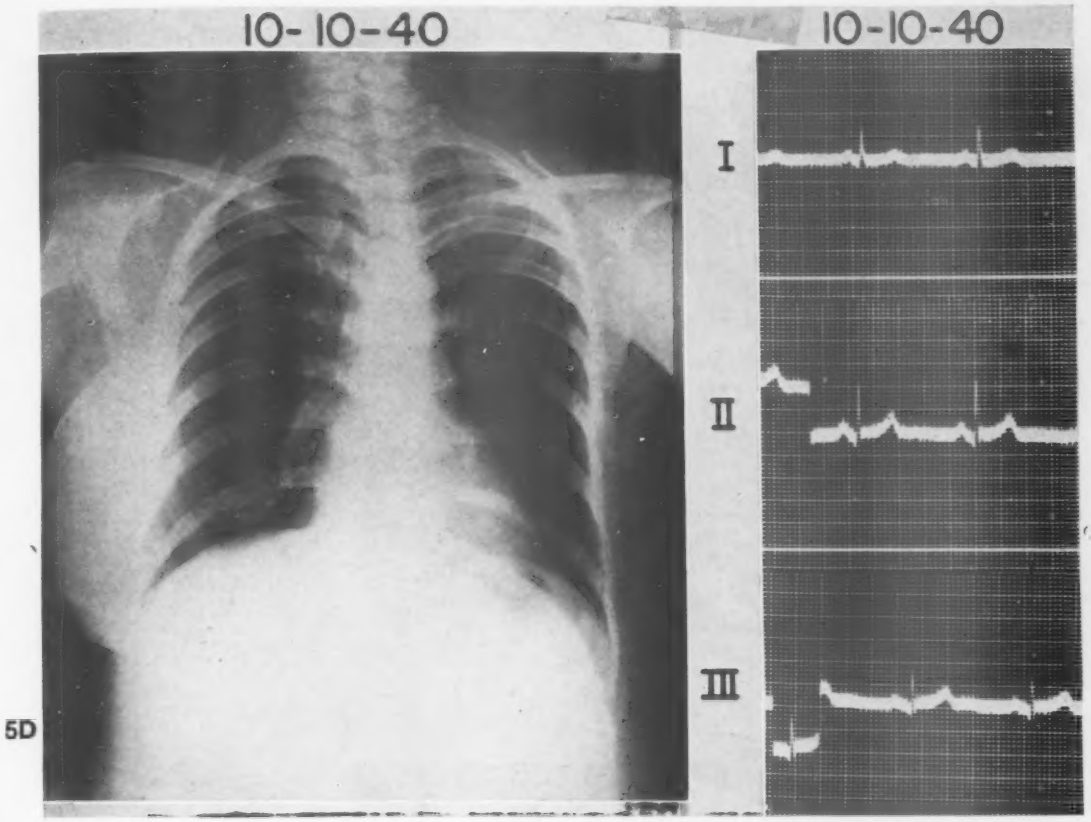


Fig. 5*D*. L. L., aged forty-three. Cancer of the left breast. Eighteen months after roentgen treatment.

in the electrocardiogram was seen in patients who were treated for cancer of the breast. These changes were limited chiefly to the ventricular complex. There were frequent changes in the voltages of the QRS complex. These occurred in serial electrocardiograms and there was often considerable variation from tracing to tracing.

The differences in the configuration of the T waves were more striking. When the left thorax was treated and an appreciable degree of irradiation pleuropulmonitis developed with its attendant mediastinal shift and rise in the left diaphragm, the T wave in Lead I became progressively lowered and even became negative in a few instances. T_3, its reciprocal, became higher (Fig. 5). Conversely, when the right thorax was treated, T_1 became higher and T_3 lower. These latter changes were not as marked as when the left thorax was treated.

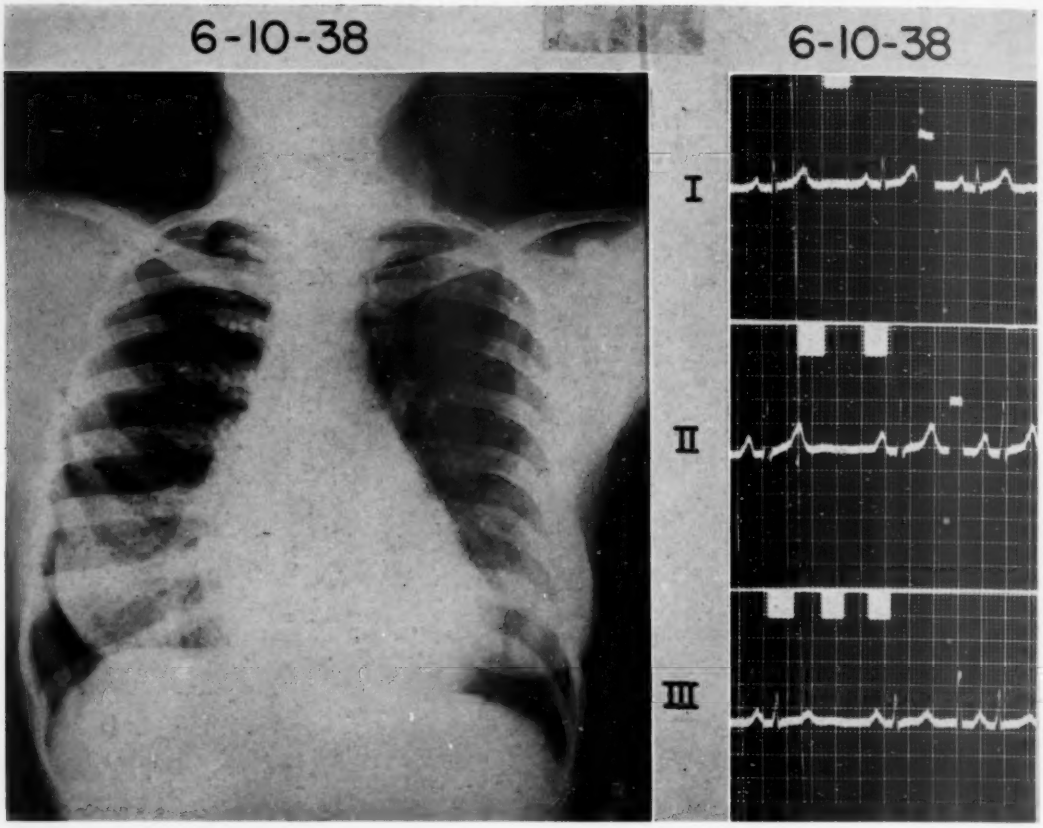
However, when the mediastinum received the bulk of the irradiation, as it does in patients with cancer of the lower esophagus, the electrocardiographic changes were the least marked and consisted of only minor variations of the voltages of the different waves.

To summarize these findings, the following results have been obtained.

(1) At the height of the irradiation reaction the blood pressure frequently falls. The reasons for this have already been discussed.

(2) A carotid sinus syndrome may develop when infected cervical nodes containing metastatic cancer have been treated.

(3) The venous pressure may be elevated and the circulation-times may be prolonged.



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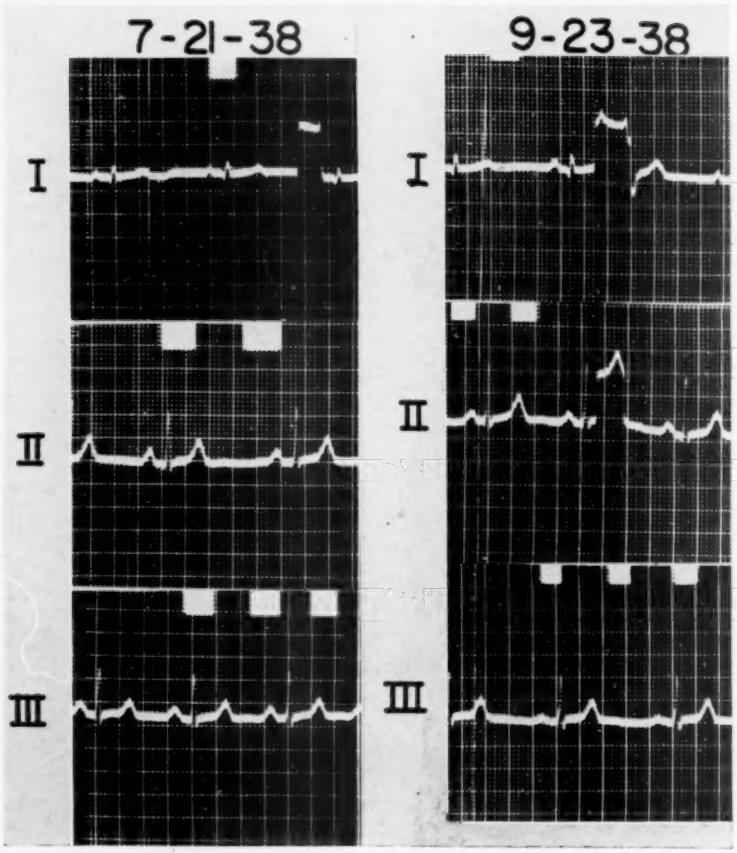

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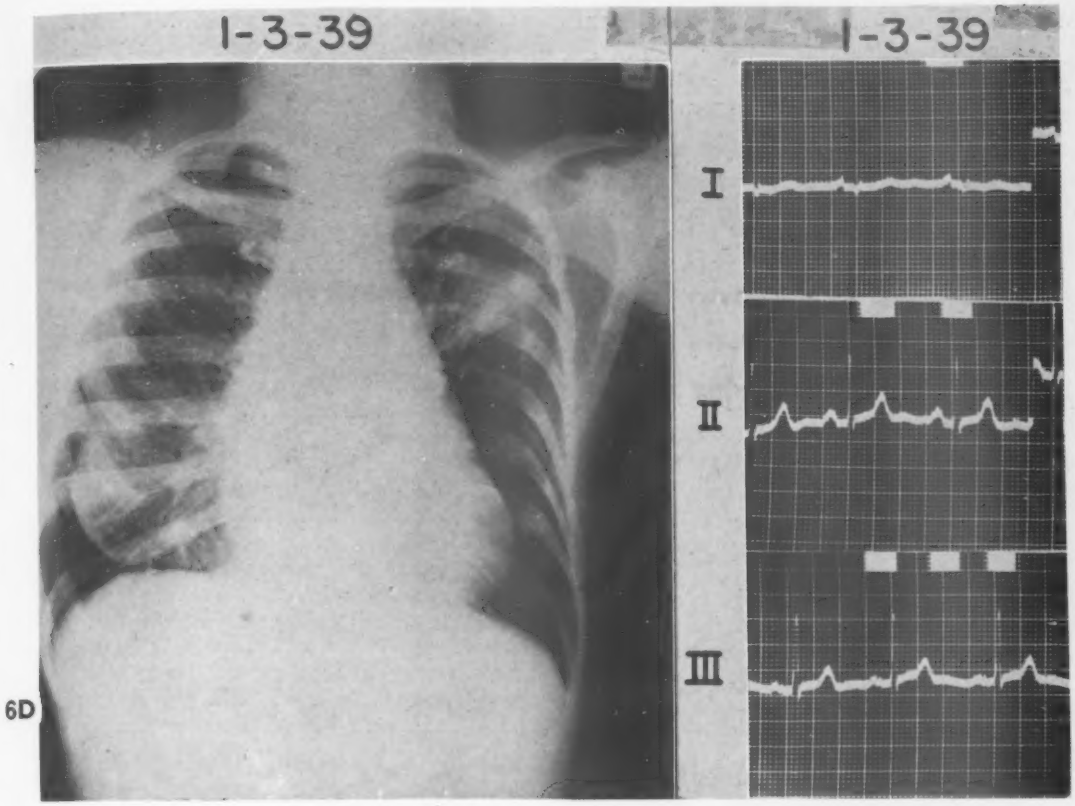

Fig. 6. R. W., aged thirty-seven. Cancer of the left breast, rheumatic heart disease. *A*, before treatment; *B*, after mastectomy; *C*, after roentgen therapy; *D*, seven months after operation, four months after roentgen therapy. Note the decrease of T_1 and corresponding increase of the voltage of T_3 in patient after left radical mastectomy. The added factor of chronic irradiation pleuropulmonitis(1-3-39)has aggravated these changes but little.

(4) Chronic pericarditis or pleuropericardial adhesions may rarely develop following roentgen therapy to the chest. However, from previous as well as our own animal experiments, it is evident that the pericardium resists single doses up to 10,000 r.

Work now in progress indicates that even when only a portion of the lung is subjected to roentgen therapy, the remainder of that lung may be affected by a secondary inflammatory reaction. All radiologists are familiar with diaphragmatic adhesions following a roentgen-ray cycle to the axilla. They are also familiar with the marked mediastinal displacement that can occur with irradiation fibrosis. The scope of the pulmonary reaction is all out of proportion to the original volume of lung exposed.

A more likely explanation for the cause of the pericarditis and adhesions between the pericardium and the lung is extension of an inflammatory reaction to the pericardium from the contiguous lung.

The progressive changes in the electrocardiogram are confusing and superficially might be taken to indicate the occurrence of myocardial disease sequential to the roentgen therapy.

Electrocardiogram. The configuration of any electrocardiogram depends on (1) the manner in which the excitation wave is conducted through the heart, (2) the physiologic state of the myocardium, and (3) the direction of the pathways conducting the action current from the epicardial surface of the heart to the extremities.

Einthoven, Fahr and de Waart[7] and Meek and Wilson[17] and others[1,2,3,14,19] have

recorded changes in the electrocardiogram as a result of changes of the position of the heart in the chest. Katz and his co-workers[11,12,13] have clearly shown that the bulk of the action current is carried away from the heart by the left diaphragm, posterior thoracic muscles and the lower left anterior chest.

The changes in the relationship of the heart to these structures may be quite marked when the left lung is irradiated. When the right lung is treated the disturbances of these relationships are less marked. When the mediastinum is treated the relation of the heart to these structures is disturbed least of all.

It must be inferred from these findings that the electrocardiographic alterations are due to changes in the direction of the electrical pathways and are not the result of myocardial disease. In fact, similar but less marked electrocardiographic changes may occur in patients who have had a radical mastectomy without any radiation therapy whatever (Fig. 6). Moreover, none of these patients develop symptoms of heart disease. Their symptoms and signs are all due to pulmonary fibrosis.

CONCLUSION

We have found numerous instances of disturbances of the heart and circulation following roentgen therapy for the treatment of cancer in different regions of the body. These, however, do not seem to be the result of the action of the roentgen rays themselves on the heart but are rather the result of other unavoidable factors incident or sequential to radiation therapy or the cancer itself. We have no evidence that the heart itself has been damaged by the roentgen therapy as it is used today in the treatment of cancer.

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DISCUSSION OF PAPERS BY DRS. WAMMOCK AND ARBUCKLE, AND LEACH

Dr. George E. Pfahler, Philadelphia. I would like to emphasize the point that we have done much excellent work with irradiation and are now taking up the consideration of tissue damage. We must realize that in all this radiation work we are likely to be involved with some complications. This spontaneous or pathological fracture of the ribs is one of these complications that we may have to expect.

I would like to emphasize, however, that we should keep certain principles in mind always, and one should determine first just as accurately as possible the extent of involvement or the likely route of involvement and be as careful as possible to protect every bit of normal tissue that we can and that means 3 cm. or 2 cm. or 1 cm.; if it is unnecessary to irradiate that portion of normal tissue, let us keep away from it. At least that is the principle that I follow.

I have used Keynes' technique for irradiation of the breast. I think I have had one case in which secondary fracture of the ribs occurred. I have had eight or ten fractures of this kind but nearly all of them have occurred following the use of roentgen rays. Therefore, it is not an accident or complication that occurs particularly as a result of gamma rays; it occurs from irradiation whether it be gamma rays or roentgen rays, and I think that the basic element of protection is the most important thing.

I have been bothered more with the secondary neuritis that comes from the implantation of the radium needles in the neighborhood of the axilla or the infra- or supraclavicular regions, and I have now decided, when I use these radium needles, to use them in the palpable disease to get a more intensive effect on that local area and depend upon roentgen rays for the general distribution of irradiation.

I think if we keep those things in mind we will avoid some of these accidents that do occur.

I have never seen any clinical evidence of damaging effects on the heart but again I keep the rays away from the heart and from the large blood vessels as much as possible by using tangential rays—for one reason to avoid the irradiation sickness that increases if the large blood streams or large collections of blood are irradiated.

Dr. John F. Hynes, Wilmington, Delaware. To the best of my knowledge we have had no such fractures of the neck of the femur in patients treated for cancer of the uterus in approximately 200 cases which we attribute to the fact that we have always avoided the neck of the femur by the use of semicircular pelvic fields in place of rectangular fields.

Five or six years ago we worked out the advantages of semicircular fields for irradiation of the pelvis. These fields include the iliac vessels and the parametrial structures but do not irradiate the groin, which tolerates irradiation poorly, and do not irradiate the neck of the femur. These fields are as effective as the rectangular fields and spare the patient a good bit of irradiation.

We have seen other types of osteo-radionecrosis, as in the mandible, but we have not seen osteo-radionecrosis in the bones of the pelvis and in the chest wall.

In the case of the thoracic wall, most of our irradiation has been given postoperatively—a technique described before this Society some five years ago in which the treatment is confined to the parasternal area in a small, narrow strip to include the chain of nodes along the

internal mammary artery and to the supraclavicular fossa. We are opposed to irradiation of the entire hemithorax if the patient has had adequate surgical treatment.

DR. H. H. BOWING, Rochester, Minnesota. May I add the thought that it is not necessary to obtain an initial intensive erythematous reaction in the field of treatment in order to produce these distressing latent skin changes. Evidently, some patients are sensitive to the therapeutic rays, in that erythema was not noted after the treatment; yet, in later years, latent skin changes occurred. Also, the element of time seems to be necessary in that these latent changes require an interval of many years for their development. In other words, the point I want to emphasize is that no matter how carefully treatment is planned and applied, these characteristic tissue changes will occur in some cases. Furthermore, I am in accord with Dr. Pfahler's remarks that these latent cutaneous changes are more likely to develop among patients receiving heavy and repeated irradiation. Therefore, we should confine our intensive treatment to the local lesion. We, too, have observed late changes in other structures in the field of treatment; for example, in the long bones. In the case I have in mind, an infant had an extensive hemangioma, apparently involving the soft parts of the lower leg. Treatment with highly filtered radium was given at a distance. The initial result was satisfactory, and seemed free of the initial cutaneous erythema; however, in later years shortening in the affected limb developed.

Concerning the opportune time for treatment, our plan, for example, in cancer of the uterus, is to administer radium treatment designed for "cure" or palliation at the initial visit. It is our belief that this time, rather than any other subsequent visit, is the best suited for treatment. A well-planned radium treatment to meet the needs of the individual patient is outlined and as a rule carried out. It is hoped the patient will derive the utmost from our first procedure; if subsequent treatments are indicated, they are usually limited in application. We have found this method of management satisfactory.

As to the radium needle technique, and for example, the Keynes method of treating cancer of the breast, we are not equipped to employ his technique. We have placed needles containing radium sulfate and gold seeds containing radon in selected patients, usually in those who had recurring malignant lesions, and this was especially true of treatment in our early experience. Today, we prefer to apply radium surface packs with varying amounts of filtration, distance, treatment time, and the like, at the initial visit, and reserve the puncture or needle technique for some subsequent period of treatment if it is found necessary to control the local lesion.

DR. JACOB R. FREID, New York City. At the Montefiore Hospital, we have frequently observed, in the field of irradiation, bone changes and sometimes fractures when the total dosage was high. These occurred in patients surviving for long periods after the treatment was given. Fractures were most common in irradiated ribs and also in the clavicle at the junction of the middle and outer thirds where the bone is thinnest. Massive doses, especially if repeated and at close intervals, are apt to produce such injuries, even if the total dosage is not high, judged by today's standards. Although less likely to occur with small fields, the size of the field is not the determining factor. I had one patient with a local recurrence in the left infraclavicular region following a radical mastectomy for cancer of the breast, who was given 3,200 r in air, high voltage roentgen therapy, divided dose technique, to a field 6×9 cm. partially overlying the clavicle. About two years later, she developed a radiation osteitis followed by a fracture of the clavicle in the area treated. We have never observed fractures following postoperative, prophylactic irradiation for cancer of the breast.

DR. WAMMOCK (closing). The purpose of this presentation is to call attention to the fact and to present further evidence that normal bone is extremely vulnerable to irradiation. The injury in this group of cases was due to gamma irradiation. The technique described was for the purpose of showing the distribution of the radium needles. I agree that this method of treatment is difficult from the standpoint of the proper distribution of the needles. The results do not justify the continued use of this treatment except in certain selected cases.

Vol. 50, No. 5

MODIFICATION OF RADIOSENSITIVITY OF THE SKIN

VI. EFFECTS OF COMPRESSION AND LOW TEMPERATURE ON THE ROENTGEN IRRADIATION REACTION OF HUMAN SKIN*†

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IOWA CITY, IOWA

ONE of us (H. D. K.) has had the impression for several years that areas irradiated with the radiation cone pressed tight against the skin produced less reaction than if the cone just made contact during the treatment. This observation is, of course, in agreement with a corollary to the well known generalization of Bergonié and Tribondeau[1] that decreased metabolic rate decreases radiosensitivity and it is also supported by the results of several experimental and clinical investigations.[3,4,5,9,16,17] Preliminary studies* produced some evidence in favor of this impression but the results were not consistent enough to justify an extensive investigation at that time. However, the striking effects of reduced circulation in experimental animals obtained in this laboratory[6,7,8,9] have given enough encouragement to warrant additional study on the human skin.

It has been found that the radioresistance of the skin of newborn rats is greatly increased by chilling the animal to, or near, 0° C. during the irradiation.[6] The threshold dosage for the production of visible injury in animals whose temperature has been reduced is about 1,200 roentgens higher than that for animals irradiated at room temperature. The ratio of the dosage at low temperature to the dosage at room temperature required to produce the same amount of injury decreases from about 5 (at 1,500 r) to 2 (at 3,300 r).[7] It has also been found[8] that the radiosensitivity is increased proportionately as the temperature is raised from 0° to 40° C. The results of a recent investigation[9] indicate that the resistance of the skin of newborn rats is increased by mechanically blocking breathing and by ligating the tail or foot during irradiation. The above mentioned effects of low temperature and ligation are also true for older animals. These results, together with those reviewed by Carty,[3] and Ellinger,[5] serve as the experimental basis for the clinical study which will be reported briefly in this paper.

MATERIALS AND METHODS

It was decided to use the skin of patients being given roentgen therapy for cancer of the cervix uteri. This type of roentgen treatment permitted the study of anterior, lateral and posterior pelvic areas of skin. The areas were treated in pairs and the right side served as a control for the left. The radiation (200 kv., Thoraeus filtration, 1.9 mm. Cu half-value layer, 50 cm. target skin distance) was given through a 10 by 15 cm. closed-tip cone. The intensity of the radiation was about 19 r per minute, and 200 or 300 r was given at each treatment depending upon the technique used. Both areas of each pair were treated on the same day and the regions were treated in sequence so that each area was irradiated once in about five days until each one had received the desired amount of radiation. Gluteal and, in the case of radium therapy, perineal fields were also used but no attempt was made to modify the reaction of these skin areas.

RESULTS

Compression. Three pairs of areas (anterior, lateral and posterior) were studied on

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* Presented at the Forty-third Annual Meeting, American Roentgen Ray Society, Chicago, Ill., Sept. 15–18, 1942.
† The writers wish to acknowledge the cooperation of the Department of Zoology of the University in providing some of the apparatus and technical assistance.

13 patients in the first series. The cone tip was pressed tight against the skin of the left area of each pair during irradiation while the corresponding right side was treated with the cone only lightly touching the skin. Roentgen reaction varied from one patient to another and the reaction of one pair of areas sometimes varied from that on other areas on the same patient. were studied but the reactions were not recorded photographically and observations were not made frequently enough to justify their inclusion in the figure.

The skin of the first case (Fig. 1) reacted by increased pigmentation, and in all three pairs of areas, the side on which compression was used (the left) showed less reaction than the corresponding right one. The only

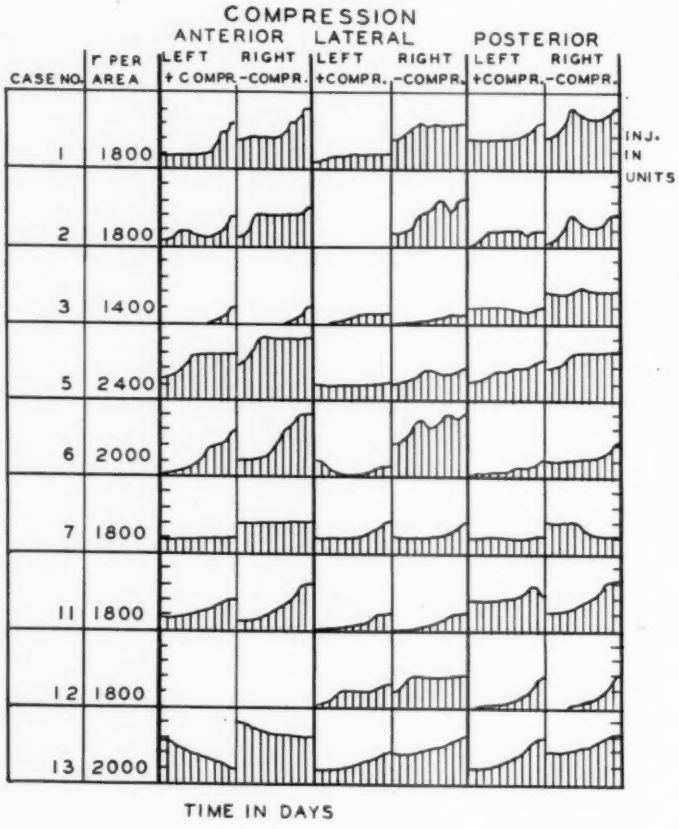

FIG. 1. A chart summarizing the data obtained in 9 cases in which compression was the means of reducing the blood circulation during irradiation. Each graph represents the amount of reaction, in arbitrary units, for ten days. Although the ten day period selected was the same for the different areas, it was not necessarily the same in one patient as in another.

The reaction usually became definitely recognizable about thirty days after the first treatment and was observed daily until the maximum reaction was apparently reached. It was difficult to measure the amount of reaction according to a standard scale. We have therefore used arbitrary units (from 1 to 4) to indicate the degree of reaction. Figure 1 is a graphic representation of the skin reaction of 9 of the patients during a ten day period when they approached a maximum. Photographs were taken to check the observations. Four other cases areas in which the difference was striking were the laterals, and one might expect that compression would be more effective in retarding the circulation because of the close proximity of the skin to bone. Case 2 was a blonde and the reaction to the irradiation was a typical erythema. Here, again, definite indication of protection with compression was evident in the lateral areas. The third patient was small and the external irradiation was not enough to produce a strong reaction in any of the areas. No definite conclusions can be drawn from this

case except that the posterior area with compression apparently showed less reaction than the side without compression. Case 4 was very slow in showing any skin reaction and the recorded data (no photographs were taken) indicated more reaction on the side with compression.

Case 5 was given heavy external irradiation and the reactions appeared early side almost continually with a possible increase in the reaction on this side. In Case 7 the reactions were not very strong but slight indications of increased resistance on the compression areas were observed on the anterior and posterior areas. The reactions on Case 8 were light and no indication of increased resistance was observed.

Case 9 showed no definite irradiation re-

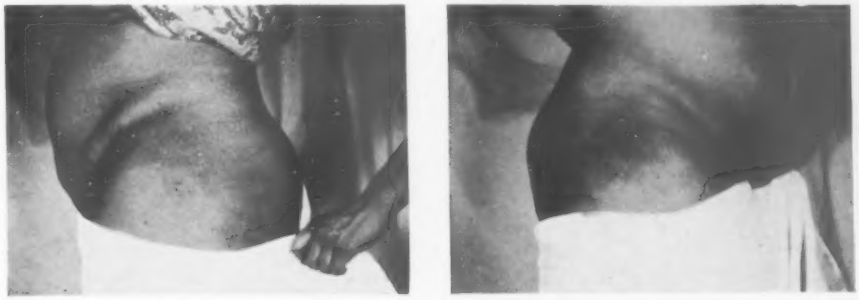

Fig. 2. Lateral areas of Case 13 on the thirty-first day after the first radiation treatment (first day of graph in Fig. 1). The left area, irradiation with skin under compression has a reaction estimated as *one*, whereas that of the right side (not under compression during treatment) is estimated as *two*.

(probably hastened by the use of a heat pad, against instructions) and reached the second degree erythema stage before subsiding. There was no striking difference in the amount of reaction on left and right sides. On the experimental side, that portion under greatest compression showed less reaction than the remainder of the area. Case 6 gave evidence of decreased reaction on the side with compression especially over the lateral fields. This result may not have been due entirely to compression during irradiation, as the patient rested on the right actions on the skin and no conclusions regarding the effect of compression could be drawn. Case 10 was very similar to Case 9. Case 11 showed more reaction on the non-pressure areas anteriorly but no difference was noted laterally and posteriorly. Case 12 was very thin, the external irradiation was less intense and no differential reactions were observed except that the right lateral showed a little more pigmentation than the left. Case 13 was very large and required heavy external irradiation. The reactions were strong and differentials in favor of the

Fig. 3. Lateral areas of Case 13 ten days after the photographs in Figure 2 were taken. The reaction has progressed in both areas but the differential in favor of the compression (left) side is still evident.

compression side were obtained for all three pairs of areas. The anterior abdominal skin areas showed strongest reactions where the overhanging abdominal skin was no doubt an irritating factor.

The Cold-tipped Cone. It was hoped that the effect of the compression could be enhanced by cooling the skin at the same time. A hollow cone tip was therefore devised which permitted a flow of water to be in close proximity to the skin. The top and bottom of the tip were of aluminum and conducted heat very rapidly. Water of the desired temperature was pumped from a large thermos jug and, after going through the tip, was returned to it. The temperature was measured by means of a constant-copper thermocouple 1 mm. in diameter and 1 cm. long placed between the cone tip and the skin. Readings were observed continuously and were recorded five times during each irradiation (0, 1/4, 1/2, 3/4, and 4/4 time). The temperature was controlled by adding warm or cold water to the thermos as needed. As soon as the temperature of the thermocouple reached the desired point, the irradiation was begun. At the conclusion of the irradiation (10 to 15 minutes in duration) the skin was allowed to return to its usual temperature.

The results of lowering the temperature are shown graphically in Figure 4. The factors of the irradiation were the same as in the compression series. The first patient of this group (Case 14) showed less reaction on the cold areas, as did Case 15. Case 16, however, failed to show any definite protective effect of the cold except for one stage of the reaction on the lateral skin area. It was apparent that none of the areas of the second series produced as much reaction as did those without compression in the first series. This was possibly due to the fact that even the right, or control, areas of the second series were under some compression, which was necessary in order to maintain the skin at a constant temperature. The protective action of the low temperature was not very evident in Case 17 but was pronounced in Case 18 which, by the way,

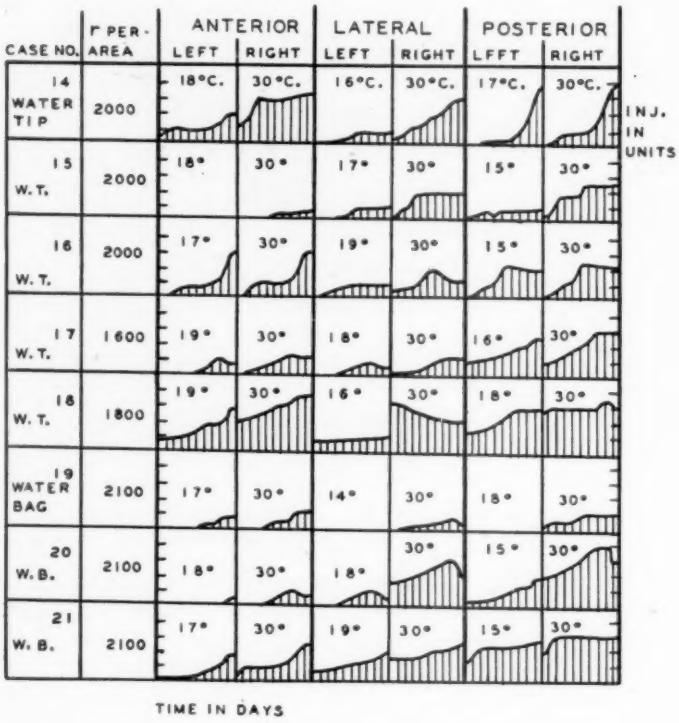

FIG. 4. A chart summarizing the irradiation reactions of 8 cases in which the circulation of the left side was further reduced by low temperature.

had a very high skin temperature. It became evident at this time that the metal cone tip was not reducing the temperature evenly over areas in which body contour was irregular. In order to meet this difficulty a rubber water bag (with circulating water at the desired temperature) was inserted between the cone tip and the skin. This allowed the entire area to be affected by the temperature of the water. The first patient so treated (Case 19) showed little reaction in any of the areas; but there was a marked indication of protection by low temperature in Case 20. In Case 21 the differential was not very definite. In Case 22, it was not possible, due to the condition of the patient, to give the full course of irradiation but the slight reaction which was produced appeared first on the lateral and posterior areas treated at 30° C.

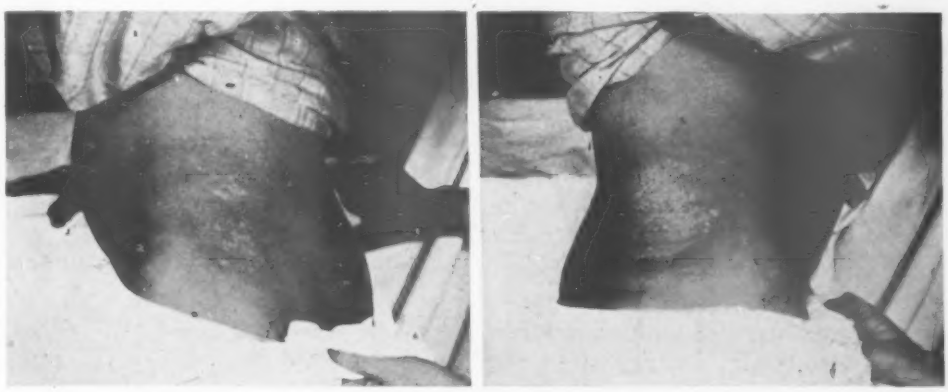

Fig. 5. Lateral areas of Case 18 on the forty-third day (tenth on graph) after the first radiation treatment. Both areas were under some compression during irradiation, but the left was at 16° C. whereas the right was at 30° C. during the treatments.

DISCUSSION

The results of these experiments were somewhat disappointing in that the compression and low temperature did not completely protect the skin in any case, and individual variation was high. It is not possible to say exactly how much protection was afforded, but when compression was used it approximated the estimation of 20 per cent increase in tolerance which was proposed by Reisner.[17] Dyes[4] estimated that pressure anemia decreased the radiosensitivity (epilation) by 40 to 50 per cent. In our experimental animals it was found that irradiation at 15° C. increased the tolerance by about 53 per cent. However, irradiation of the young experimental animals at 0° C., or with breathing blocked during the irradiation, increased the radioresistance by 300 per cent. It appears that both the characteristics of the tissue and the inadequacy of the method might have been responsible for the failure to demonstrate a greater increase in radioresistance of the skin under conditions of reduced circulation during irradiation.

It is clear that compression as was used on the skin of patients did not block the circulation as well as ligation would have, so it is to be expected that the increased resistance was not as great as that found for the skin of experimental animals in which the appendage was tightly ligated during the irradiation. Likewise, the temperature in the clinical investigation was not low enough to provide striking protection, nor would the effect of the cold water be expected to penetrate far into the human body. It is probable that some circulation was taking place in the deeper vessels even during the coldest applications. However, the low temperature, as used clinically, would be expected to extend to the periph-

eral capillaries and the temperature was low enough to reduce gaseous exchange to a minimum.[14] This would be expected to lower the activity of tissue cells. The resulting increase in radioresistance is to be expected according to the generalization of Bergonié and Tribondeau,[1] and is also in accord with the fluid-flow theory of Failla[11,12] in that extracellular circulation is reduced.

Lower temperatures might have been more effective, but one is confronted with the possibility that if the temperature is reduced too much it might in itself be harmful to the skin. A few instances of increased irradiation action as a result of long exposures to low temperature have been reported.[15,16] However, we have evidence in experimental animals[10] that low temperature is most effective during the irradiation and the resistance is not increased appreciably by low temperature before or (for short periods) afterward. It might be feasible to chill the human skin to temperatures lower than 14° C. if the radiation and temperature exposure were limited to a very short period of time.

Another limitation of the clinical study was the method of observing skin injury. In the experimental animals, histologic examinations were made which allowed quantitative comparisons of injury produced under different conditions. Observation of irradiation reaction in the clinical investigation was restricted to the appearance of the skin. Erythema is not a very satisfactory criterion of irradiation reaction but is the best available under the circumstances. The recent report of Borak[2] indicates that erythema is related to differential effects on the capillaries, arteries and veins, and only that reaction related to injury to the arteries is affected by cold or reduced circulation. Our failure to reduce completely the irradiation reaction with cold and compression may be related to the appearance of the first and third erythema. These might overlap the second erythema in time, as the therapy was fractionated.

A factor of considerable importance is the susceptibility of irradiated human skin to subsequent irritation. Several instances were noted where the irradiated skin suddenly developed a marked erythema on the posterior areas following internal radium therapy. This was probably due to the irritation and rise in temperature of the skin during the several hours the patient lay on a rubber sheet. Likewise, in several instances where the patient rested almost entirely on one side, that lateral area showed the greater erythema. The one case in which the patient used an electric heating pad demonstrated very definitely a rapid acceleration of the roentgen reaction, and may have obscured any difference due to the rate of circulation during the irradiation. It may be that trauma, heat, or irritating substances injure the cells of the human skin enough to cause liberation of histamine,[5,14] in addition to that already being liberated by the irradiation injured cells and thereby to increase the swelling and permeability changes taking place in the irradiated blood vessels. The situation is further complicated by the refractory action to histamine of the irradiated skin after the erythema has appeared.[2] Thus a skin in which the erythema is slow in forming may exhibit a reaction to irritation which might not be evident in the skin in which the erythema was already present.

SUMMARY AND CONCLUSIONS

Experimental and clinical literature contains evidence to indicate the feasibility of increasing the radioresistance of the human skin by employing compression and low temperature during the irradiation.

An attempt has been made to decrease the irradiation reaction of the skin of patients receiving therapy for cancer of the cervix. Some positive results have been obtained but the individual variation was great and the roentgen reaction was apparently affected in several instances by changes in environmental conditions following the irradiation. It is concluded that it is advisable to use compression where possible, but low temperature in addition

(as used in this investigation) is of doubtful value considering the effort involved.*

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* For discussion see page 639.

A GROUP OF PERSONS WHOSE SKIN AND SUBCUTANEOUS TISSUES ARE UNUSUALLY SENSITIVE TO ROENTGEN RAYS*

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EVERY radiologist is more or less familiar with the action of roentgen rays on the skin. It is also well known that the sensitiveness of the skin of different persons and of different parts of the body of the same person varies considerably according to its thickness in different regions, according to the degree of pigmentation, and according to previous exposure to the sun or to artificially generated ultraviolet rays. Thus, the difference in sensitiveness of the skin between a child or young adult and an aged person is well known. The difference in sensitiveness between the skin of a red-haired, blue-eyed, and freckled person and that of a Negro represents the two extremes ordinarily encountered. The skin of the average woman is more sensitive than that of the average man. Difference in thickness of the skin, the amount of pigment which it contains, and the abundance of its blood supply appear to be the three major factors which influence its sensitiveness. The nerve supply of the skin and the nervous system of the individual undoubtedly represent additional important factors. Radiologists are also aware of the increase in sensitiveness which follows the topical application of certain drugs such as chrysarobin, iodine, iodoform, mercury, sulfur and tar. Other factors, such as ischemia, anemia, or hyperemia from any cause, also influence the sensitiveness of the skin. The range of sensitiveness has been variously estimated at 15, 18 or 20 per cent.

For many years a point of controversy has been whether or not the skin of some persons is more or less sensitive to roentgen rays than that of the average person; in other words, whether the sensitiveness of their skin exceeds the 15 to 20 per cent range which has generally been taken to represent the range of average sensitiveness. Some radiologists believe that true idiosyncrasy exists, while others, especially those who have had extended experience with the use of roentgen rays for therapeutic purposes, question the existence of idiosyncrasy. An interesting fact is that the legend of idiosyncrasy has come down to use from the early days of roentgenology, when the methods of measuring roentgen rays were crude or when the quantity and quality of the rays was only roughly estimated. As time has elapsed, as apparatus to generate roentgen rays has improved, and especially as more and more accurate methods of measurement have been devised and adopted, the number of roentgenologists who believe that idiosyncrasy exists has diminished steadily. This fact in itself would lead one to conclude either that idiosyncrasy is a legend based on superficial and uncritical impressions or that, if idiosyncrasy does exist, it is much less common than it was once thought to be.

My own opinion is that, while true idiosyncrasy apparently cannot be absolutely denied, it is an uncommon or rare phenomenon and is apparently related to certain associated physiologic or pathologic factors which have not yet been clearly defined. Thus, patients who are being treated with roentgen rays for certain forms of dermatitis or other diseases of the skin, but who are also afflicted with allergic manifestations, such as hay fever, asthma, or undue sensitiveness to different foods, may sometimes exhibit more or less marked erythema of the skin after a dose of roent-

* Presented at the Forty-third Annual Meeting, American Roentgen Ray Society, Chicago, Ill., Sept. 15–18, 1942.

gen rays which, in the average person, would not cause the slightest reaction.

But the purpose of this paper is not to discuss the problem of idiosyncrasy as such. Its object is to draw attention to a group of persons who, when undergoing roentgen treatment for any pathologic condition, tend to present, sooner or later, a peculiar and characteristic reaction of the skin and subcutaneous tissues. After a single exposure to a dose of roentgen rays to the limit of tolerance, the skin reacts much like the skin of other persons except that a somewhat stronger erythema follows a smaller dose, and a greater degree of pigmentation follows the erythema. Of course, the individuals of this group vary in sensitiveness from one another according to age and degree of pigmentation. Inasmuch as this group includes blond and brunet individuals, the same variation in sensitiveness occurs among them as among other persons, as far as this factor is concerned. On the whole, however, their skin is distinctly more sensitive than the skin of persons who do not belong to this group; as an average, this increase in sensitiveness may amount to about 10 per cent.

When, because of the pathologic condition for which treatment is intended, the skin of a given region must be exposed to roentgen rays from time to time for several months or several years, and when the dose of rays at each session of treatment is maintained at the limit of tolerance, the skin becomes more and more deeply pigmented; in fact, the degree of pigmentation is considerably greater than in other persons, probably for the same reason that persons of this group acquire an unusual degree of tan from prolonged and repeated exposure to the sun.

After the treatment has been repeated three or more times, not only does the pigmentation of the skin become increasingly pronounced, but the skin and subcutaneous tissues gradually become diffusely indurated. If, in spite of this induration, the affected region is exposed to additional tolerance doses of rays, the induration continues to increase and gradually affects the underlying muscles to a certain depth. These muscles become diffusely indurated, fuse one with another, and become fixed to adjacent bones, so that they no longer function and are now only a mass of immovable tissue. Not only is muscular function abolished, but the mass fusion and induration of muscles, subcutaneous tissues, and skin, and the fixation of these tissues to underlying bones, act as a more or less complete brake on the function of adjacent normal tissues. When this effect occurs in the lumbar region, the back can no longer be bent at this level, the patient's movements are greatly limited, and his posture becomes the posture of a statue. When the sacral or gluteal region is thus affected, the patient finds it increasingly difficult to change from a standing to a sitting position, and *vice versa*. It is not difficult to realize the patient's predicament, which is that of a seriously crippled person. The constant strain of any unchangeable position is not appreciated by the average person, but it is appreciated by the soldier who, as punishment for some infraction of military regulations, is ordered to stand motionless at attention for an hour.

Needless to say, telangiectasis and superficial ulceration also may further complicate the patient's unfortunate situation.

How can this most undesirable effect be prevented? It can be prevented or minimized by recognizing the type of person before any treatment is given, by giving as little treatment as possible to obtain the desired effect on the lesions for which the treatment is required, and especially by keeping the quantitative dose of rays below the limit of tolerance. The third condition is especially important after a given region has been irradiated three or four times at varying intervals. But the most important of these three conditions is the first, that of recognizing the type of person before any treatment is given. With close observation and experience one can learn to recognize very readily persons who belong to this group. Indeed, they can sometimes be rec-

ognized in the street when fully dressed.

Those who are interested in anthropology are familiar with Sheldon's[3] classification of human beings according to the conformation of the body; in other words, according to the shape and proportions of the body. This classification has been adopted by Hooton[2] and by many other anthropologists. Physicians would do well to take an active interest in anthropology because they would find in it the solution to some of their problems. For example, after examining and measuring the scapulas of thousands of human bodies, Graves[1] found that the scapula is a valuable index of an individual's chance of living into old age. Sheldon classified human beings into three main groups: ectomorphic, endomorphic, and mesomorphic, the third and last being a blend of the two other groups.

The group of persons to which I refer corresponds to Sheldon's endomorphic group. The body has a rounded contour; that is, the lateral and anteroposterior diameters of the trunk are approximately equal. The bony framework and musculature are not developed as much as in individuals of the ectomorphic or mesomorphic type. The limbs are usually short and tapering, the hands and feet are small, and the head is round. Not only is the contour of the trunk rounded, but the extremities also are smoothly rounded, and the muscles do not stand out in prominent bulges. Arms, thighs and legs are beautifully curved. In male individuals, especially at ages between twenty and forty years, the contours of the trunk and extremities and the texture and appearance of the skin often suggest those of the female. Still more significant is the character of the skin and subcutaneous tissues. The skin has a smooth and fine texture, has the tone of fresh, soft rubber, and the hair is relatively thin or scanty, even on the scalp. Moreover, the skin and subcutaneous tissues together have the appearance and give the sensation of a firm, rubbery plumpness. In this group the sexes are about equally represented.

The first step in recognizing these individuals is a good knowledge of the general appearance and conformation of the body, its compact, rounded, and attractive shape as a whole as well as in its different parts. The reader must not infer that all individuals with a body conformation of endomorphic type exhibit this feature to the same degree; far from it. The degree of endomorphism, in fact, varies with each individual. This feature is more prominent in some individuals than in others, and many gradations exist between this group and the two other groups of Sheldon's classification.

The other and most important feature from the standpoint of sensitiveness to roentgen rays is the smooth, clear or semitranslucent appearance of the skin and its exceptional tone, as if a certain proportion of the best quality of rubber entered into its composition. It is a skin which is pleasant to look upon and to touch. The subcutaneous tissue also has an unusually firm and rubbery consistency, so that, when it is taken between the fingers and thumb, it has an unusual resiliency. The relative proportion of these features is a measure of radiosensitiveness in comparison with other persons.

Once the ability to recognize this type of person beforehand has been acquired, the exceptional sensitiveness of the skin and subcutaneous tissues should always be kept in mind. From the very beginning, the roentgenologist should be careful to give to such persons as little roentgen treatment as possible; in other words, to give only as much treatment as may be necessary to control the lesions treated. When a so-called tolerance, or erythema, dose is required, the quantity of rays should be only such as can produce a minimal degree of erythema. Still more essential is that, as time goes on, the treatment be repeated as seldom and at as long intervals as possible. After the patient has been treated three or four times, it becomes increasingly important to diminish the quantitative dose subsequently given to each field. A reduction of 10 per cent may be sufficient, but this depends on the quan-

tity of roentgen rays which each roentgenologist has chosen as his limit of tolerance.

The foregoing considerations do not apply so much to roentgen treatment given by the fractional method because, as is well known, this method represents an attempt to achieve, by one bold stroke, complete regression and a permanent cure when a malignant process is not extensive. Fractional irradiation with a maximal total dose may not be repeated safely more than once, and even then the total dose given the second time should be somewhat smaller than that of the first time. But when a roentgenologist elects to treat a chronic inflammatory or malignant lesion by giving subtolerance doses by the fractional method or by the method of full treatment of each field in one or two daily sessions, the considerations which I have attempted to set forth may have the greatest significance.

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DISCUSSION OF PAPERS BY DRS. EVANS AND KERR, AND DESJARDINS

Dr. Erich Uhlmann, Chicago. It is a great privilege to be asked to discuss these two papers presented by Dr. Desjardins and Dr. Evans and Dr. Kerr. Dr. Desjardins has presented to us his experience which is based on a very great number of observations. He was kind enough to send his paper to me some time ago and I have looked at my patients with a different eye since that time, trying to recognize the group of patients whom Dr. Desjardins described to us.

In addition to what he presented today, he mentioned in his paper a few facts which he calls minor but which, I think, are quite important because he draws attention to facts which we all have accepted and which are familiar to us but which after all might not be so well established facts. He mentions, for example, the difference in the sensitivity of the skin of adults and children and it is generally accepted that the skin of small children is much more sensitive to radiation than the skin of adults.

Several years ago I did some experiments exposing the skin of children to an amount of radiation sufficient to produce erythema. Much to my surprise many of these children did not develop erythemas on their skin following such exposure. The dosage for these children could be increased and they could be given much more radiation than adults. It may be that the skin of some children is more sensitive than that of adults but I do not think it possible to make that a general statement. Besides, it is certainly a fact that the skin of young persons has much greater potentialities and tendency for recuperation from radiation effects than the skin of the adult.

After reading this paper of Dr. Desjardins, I had some of the children who were treated for malignant tumors some years ago come back to the hospital to be examined. The skin of these children, who received in some instances single field doses of over 3,500 roentgens, was absolutely normal. It did not show any discoloration up to three or four years following such extensive irradiation. I therefore think we might revise some of our concepts in this matter.

There is not enough time to go into more details but I can just mention Dr. Evans and Dr. Kerr's paper. I had the provilege of seeing this paper, also, before it was presented here. In addition to his work shown here today, Dr. Evans has done considerable work on animals which, I think, is quite impressive. The slides shown here may not reveal much difference in the skin reactions observed in human beings but I presume that this is only a beginning.

Several years ago when I worked on related problems I tried to explain these phenomena on the basis of a summation effect. I thought that the changes in the capillary system and circulatory changes might be responsible for the higher or lower degree of sensitivity to irradiation. Dr. Evans, who did not go into any discussion of this problem today, although he mentions it in his written paper, thinks that it is an effect of metabolism rather than anything else. Whatever the answer is, I believe that Dr. Evans will agree with me that further experiments are necessary to explain these features.

DR. DESJARDINS (closing). I want to thank Dr. Uhlmann for his comments. I am especially interested in his comment about the skin of children; he is perfectly right in saying that the skin of children, at least beyond three years of age, can tolerate irradiation as well if not better than that of adults. In many cases the skin of young children tolerates irradiation better than that of most adults. In my paper I did not compare the skin of children with that of young or middle aged adults. I compared it with that of aged persons, and by that I meant not so much aged in the sense of years as aged in the quality of the skin. As you know, some persons at seventy years of age are younger than others at fifty, and *vice versa*. Sometimes the skin of an old person can take treatment as well as that of a person aged thirty years. On the other hand, when a person reaches a certain age, say sixty years, or at some time or other after that age, the skin begins to lose its tone; it begins to show varying degrees of atrophy, and the circulation of the skin alters gradually. Then, a considerable difference in radiosensitiveness or rather an increasing resistance to roentgen rays may be noticed. That is all I meant by my reference to it in the paper.

Vol. 50, No. 5

THE EFFECT OF ROENTGEN RAYS, RADON AND RADIOACTIVE PHOSPHORUS ON THIAMIN CHLORIDE*

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THE possible destructive effects of radiation on the thiamin molecule have never excited serious investigative interest even though thiamin has been advanced as a useful medicament in the treatment of irradiation sickness.[2,4,7,14] The favorable therapeutic results have been judged for the most part on rather poorly controlled clinical trials and some investigators have found thiamin to be of limited value.[11] If thiamin therapy produces good clinical results it would be desirable to understand the underlying mechanism or, if the results are unsatisfactory, to know whether this approach should be abandoned.

To date, the rationale of thiamin therapy in irradiation reactions rests for the most part on a rather strained analogy between the symptoms and pathology of vitamin B deficiency and those of irradiation injuries.[1,8] No crucial animal experiments have been conducted[8] and only a few investigations have been reported on the direct effect of radiation on vitamin B. Funk,[3] in 1916, found that exposure to radium had no effect on the beriberi or growth-promoting factors of vitamin B complex. Karczag and Hanák,[5] however, described a change in the ultraviolet absorption spectrum of vitamin B_1 after exposure to roentgen rays, and Kögel[6] found that roentgen irradiation induced a barely perceptible change in vitamin B_1 as judged by silver reduction. Sugiura[12] and Sugiura and Benedict[13] showed that the growth-promoting factor in yeast could be destroyed by exposure to radium emanation and that roentgen irradiation of wheat reduced its growth-promoting effect as tested on rats fed a vitamin B deficient diet. In our experiments we have attempted to determine whether crystalline thiamin chloride in aqueous solutions or tissue thiamin is subject to destruction by different forms of ionizing radiation.

EXPERIMENTAL

Merck's synthetic crystalline thiamin chloride in distilled water, 100 milli-micro mols per cubic centimeter was used for *in vitro* experiments. Two cubic centimeters of this stock solution was exposed to various doses of radon, roentgen rays, and radioactive phosphorus.

Roentgen exposures were carried out with the solution in glass test tubes having a wall thickness of approximately 1 mm. Varying dosages were used at 200 kv. and at 1,000 kv. In the case of the 200 kv. irradiation, a filter of 0.25 mm. Cu was used and a target distance of 12 cm. In the 1,000 kv. exposures the test tubes were placed above the filters as close to the target as was feasible, in order to deliver a very large dose in a reasonable period of time. Under these conditions no accurate dosage measurements were possible and the stated dose is subject to an error of at least 20 per cent. In certain instances lead filings were dropped into the test tube in an attempt to obtain scattering of the rays and an increased effect.

Radon exposures were accomplished by dropping a sealed glass capillary containing from 10 to 20 millicuries of radon directly into 2 cc. of the thiamin chloride solution in a small test tube. The capillary was allowed to remain long enough to obtain the desired dosage when it was removed and the tube tightly stoppered.

Exposures to radioactive phosphorus (P^{32}) were accomplished by placing a meas-

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ured amount of an aqueous solution of Na_2HPO_4 containing P^{32} in the bottom of a test tube, evaporating to dryness and then adding 2 cc. of the stock solution of thiamin chloride. These tubes were sealed and allowed to stand for thirty-two to forty-three days before testing. During this period a large proportion of the initial radioactivity was dissipated by the natural decay of the P^{32}. In order to control any effect that might be exerted by the Na_2HPO_4 apart from its radioactivity or any effect of the residual radioactivity at the time of assay, control tubes were set up in identical fashion except that the thiamin solution was added immediately before assaying.

The thiamin assays were carried out in part by the *Phycomyces* method originally proposed by Schopfer and Jung[10] and since used by numerous investigators, and in part by the *Phytophthora* method.[9] In both methods, a small inoculum of the mold is placed on a medium containing only simple salts and sugar to which is added a measured quantity of the sample to be tested. The dry weight of the mold mycelium which grows in seven days in the case of *Phycomyces* or forty days with *Phytophthora* bears a strict relationship to the amount of thiamin or its intermediates available in the medium. The amount of thiamin in the sample may then be estimated by comparison with parallel assays on samples of known thiamin content.

The two molds differ in that *Phytophthora cinnamoni* requires molecular thiamin for its growth, whereas *Phycomyces blaksleeanus* grows equally well if supplied with molecular thiamin or with equivalent amounts of the thiamin intermediates, thiazole and pyrimidine. Both methods are sensitive to extremely small quantities of thiamin. The *Phycomyces* assay should give reproducible results with an experimental error of less than 10 per cent, while the *Phytophthora* assay is somewhat less dependable. Assays of urine, blood or tissue emulsates do not give dependable results since extraneous substances may interfere with the growth of the molds.

RESULTS

Exposure to Roentgen Rays. Four glass test tubes with a wall thickness of approximately 1 mm. each containing 2 cc. of thiamin chloride solution were exposed to roentgen radiation generated at 200 kv. and 6 ma. with a filter of 0.25 mm. Cu and at a target distance of 12 cm. The exposure times were 10 min., 20 min., 25 min., and 30 min. and the four tubes were exposed to doses of 5,000 r, 10,000 r, 12,500 r, and 15,000 r, respectively. In no case did the assays show any decreases in thiamin activity as compared to the controls. Another sample exposed to 9,000 r under similar conditions but with a different machine showed a very slight loss of activity which probably falls within the error of the assay method.

Still another sample of thiamin chloride was exposed to 30,000 r ($\pm$ 20 per cent) at 1,000 kv. and showed no loss of activity. In an attempt to increase the scattering of this short wave length radiation within the solution, washed lead filings were added directly to a similar sample and given the same exposure under the same conditions. This tube showed a loss of 70 per cent of its thiamin activity. Similar tubes were exposed to 9,000 r at 200 kv. in the presence of lead filings, in the absence of lead filings, and to lead filings alone without irradiation. Roentgen irradiation alone produced an insignificant decrease in thiamin activity; lead filings without irradiation caused a 70 per cent loss of activity and lead plus irradition produced a further drop in activity to 10 per cent of the control value. It is thus apparent that roentgen irradiation alone as it was administered had little effect on thiamin chloride, but that lead alone produced a profound loss of activity which could be augmented by superimposed irradiation. On adding lead filings to unirradiated thiamin solutions, a fine white precipitate formed which was soluble in 5 per cent nitric acid.

Exposure to Radon. In five different experiments a total of twelve samples of thiamin chloride were exposed to different doses of radon. Nine of the samples were assayed with a strain of *Phycomyces* maintained at

the Boston Children's Hospital and the other three were assayed with *Phytophthora* at the New York Botanical Garden. The results obtained at the two laboratories are presented in Table 1. They are not in agreement quantitatively although qualitatively there is evidence of a progressive loss of thiamin activity with increasing doses of radon. The actual curves obtained in one group of *Phycomyces* assays on thiamin exposed to radon are presented in Figure 1.

The "dose" of radon as stated in these experiments has a deceptive appearance of significance. The activity of the radon capillaries was carefully measured and the exposures were accurately timed so that the "doses" fairly represent the amount of radiation *delivered* by the radon. However, the amount of energy *absorbed* by the test object is the important factor in work of this nature. It is obvious that a small source of energy such as a radon capillary lying in the bottom of a test tube will expose the fluid in various parts of the tube to very different amounts of radiation. The fluid in

Table 1

Children's Hospital Assays (*Phycomyces*)		Botanical Garden Assays (*Phytophthora*)	
Dose of Radon (mc-hr.)	Percentage Destruction of Thiamin	Dose of Radon (mc-hr.)	Percentage Destruction of Thiamin
38	14	50	50
64	33	300	90
89	18	700	100
91	18		
286	30		
512	55		
585	67		
670	97		
2650	96		

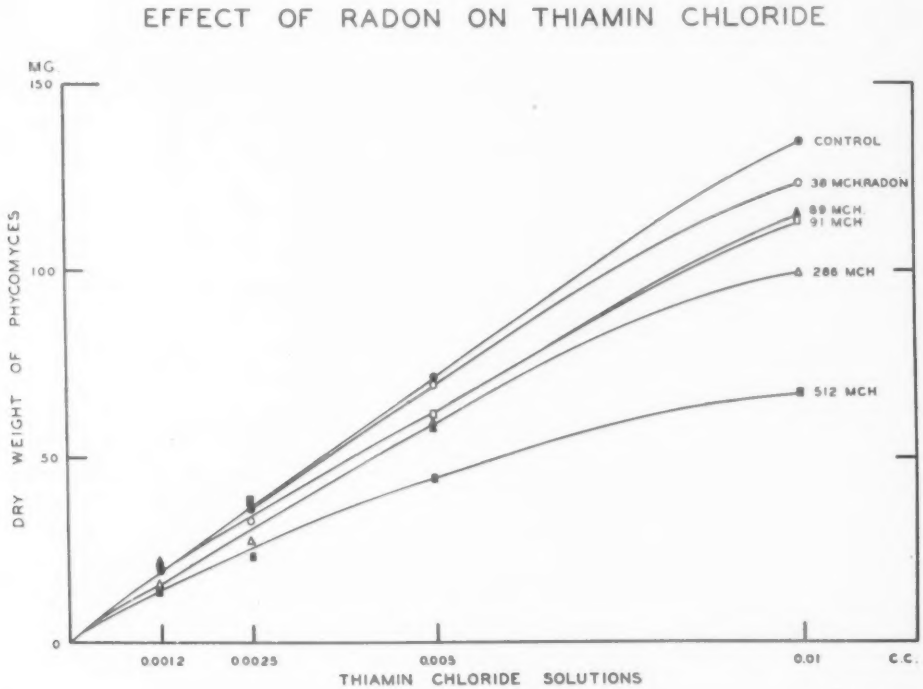

Fig. 1. The graph represents *Phycomyces* assays for thiamin on six samples, all taken from the same stock solution of 100 milli-micro molar thiamin chloride and differing only in the exposure of five of them to the doses of radon indicated at the right. The amount of each solution added to the standard *Phycomyces* culture medium is indicated on the abscissa and the resulting growth of *Phycomyces* in milligrams dry weight on the ordinate. Each solution was tested at four dilutions on different cultures. The curves show progressive loss of thiamin activity with increasing doses of radon.

contact with the radon capillary will be exposed to a high intensity of radiation while in the remote parts of the test tube the intensity of radiation will be decreased as the square of the distance from the source. Another difficulty in dosage measurements arises from the nature of the radiation. Radon emits alpha, beta and gamma radiation, the greater part of the energy being in the form of alpha and beta particles. The glass capillaries containing the radon have a wall thickness sufficient to absorb most of the alpha particles, a portion of the beta particles, but very little of the gamma rays. Thus the amount of energy which reaches the surrounding fluid is determined by the thickness and the coefficient of absorption of the capillary wall surrounding the radon and is significantly less than the theoretical amount of energy emitted by the enclosed radioactive material. These and other difficulties are involved in any statement of dosage from radon and radium sources. Since the conditions of exposure were kept constant in our experiments, the stated doses are quantitatively comparable even though they have limited significance in absolute terms.

Exposure to Radioactive Phosphorus. Six samples of thiamin were exposed to the action of P^{32} by dissolving radioactive phosphate directly in the thiamin solutions. The results presented in Table II show that exposure to this form of radiation also resulted in partial inactivation of thiamin. The curves obtained in the *Phycomyces* assays are presented in Figure 2.

The doses stated in these experiments are based on physical measurements but are not comparable to similar doses of radon. In the radon experiments, a concentrated source exposed various parts of the test solution to intensities of radiation which decreased geometrically with the distance from the source. In the case of P^{32} the source of radiation was uniformly diffused throughout the test solution. Even more important is the fact that the "microcurie" has been adopted as a universal but misleading unit for stating the radiation intensities of all manner of radioactive substances. One microcurie of two different radioactive substances such as radon and P^{32} may represent entirely different amounts of energy emission since the microcurie may be defined as 3.5×10^4 atomic disintegrations per second, regardless of the number, the nature or the energy of the particles or rays emitted. P^{32} in its disintegration emits only beta particles with an average energy of about 700 electron kilovolts. Radon, in equilibrium with its decay products, emits a whole series of alpha, beta and gamma radiations at widely differing energies.

TABLE II

	Initial P^{32} Activity	Time of Exposure (days)	Dose (mc-hr.)	Percentage Destruction of Thiamin
Children's Hospital Assays (*Phycomyces*)	1 microcurie	43	0.4	20
	10 microcuries	43	4.4	32
	50 microcuries	43	22.1	58
Botanical Garden Assays (*Phytophthora*)	1 microcurie	32	0.4	0
	10 microcuries	32	3.9	40
	75 microcuries	32	21.6	40

The Chemical Nature of the Change Induced in the Thiamin Molecule. It was mentioned above that *Phycomyces*, unlike some other molds and most higher forms of life, does not require the intact thiamin mole-

cule for normal growth but is able to synthesize the required thiamin from thiazole and pyrimidine. Neither of these components alone is effective and growth is determined by the amount of thiamin theoretically obtainable through combination of the available thiazole and pyrimidine. The *Phycomyces* assay method would therefore be safe to assume that thiamin had been split to thiazole and pyrimidine and that the pyrimidine had remained intact while some of the thiazole had been destroyed. On the other hand, if neither the addition of thiazole or of pyrimidine to an irradiated sample increased its thiamin activity, is would appear that the thiamin molecule at

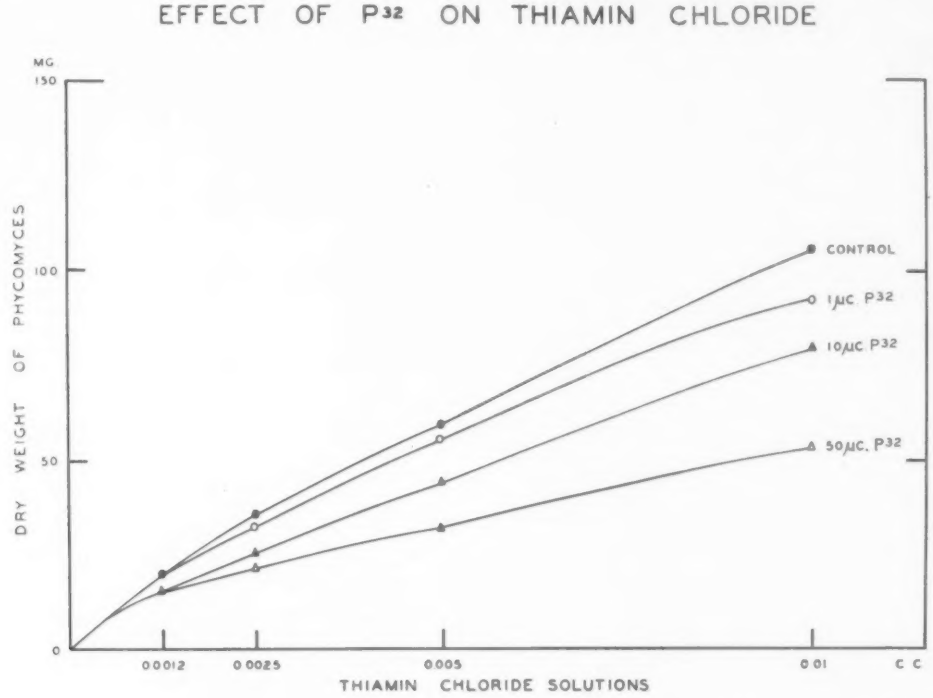

Fig. 2. The graph represents thiamin assays on standard solutions of thiamin chloride exposed to the action of radioactive phosphorus (see legend, Fig. 1). Each solution was exposed for forty-three days to the amount of radioactive phosphorus indicated at the right. Increasing doses resulted in progressive inactivation of thiamin.

not distinguish between intact thiamin and thiamin broken down to thiazole and pyrimidine. However, if irradiation should break down thiamin to thiazole and pyrimidine and then produce a further degradation of one of the components, leaving the other intact, it would be possible to determine which component was destroyed by supplementing the irradiated solutions first with thiazole and then with pyrimidine. If added thiazole, let us say, restored the growth-promoting action of an irradiated sample to the control figure, it would then a whole had been altered or that its two component parts had been separated and equally degraded. Tests of this nature were carried out.

A sample of thiamin chloride solution whose activity had been reduced to about 4 per cent of the initial value by exposure to 2,650 millicurie-hours of radon was supplemented by the addition first of thiazole and then of pyrimidine. In neither case was there any increase in thiamin activity as tested by *Phycomyces*. It therefore appears that the inactivation of thiamin by irradia-

tion does not proceed by cleavage of the molecule into thiazole and pyrimidine followed by selective degradation of one of these parts. It is more probable that the thiamin molecule is attacked at some point other than the thiazole pyrimidine linkage.

Animal Experiments. Two trial experiments were carried out to discover whether irradiation would produce significant changes in the thiamin content of the blood and livers of living mice.

Ten female Swiss mice six months old and weighing approximately 20 gm. each were exposed to a dose of 800 r of roentgen rays generated at 200 kv. In our hands this dose delivered to the whole body has proved lethal for mice within two weeks after exposure. Two days after exposure the mice were killed and pooled samples of blood and of livers collected. Similar samples were collected from 10 control mice. *Phycomyces* assays of the thiamin activity of these samples showed no significant differences between the blood and livers of the control and the irradiated mice.

A similar experiment on 5 mice each injected intraperitoneally with 34.4 microcuries of P^{32} and killed after twenty-four hours also gave negative results.

As has been mentioned, the *Phycomyces* assay method is not very satisfactory for biological material such as blood or organ emulsates. While we do not trust the values for absolute thiamin content obtained in these experiments we do believe it is significant that the livers and blood of the irradiated mice gave the same values as the unirradiated controls.

DISCUSSION

Definite inactivation of aqueous solutions of crystalline thiamin *in vitro* by radon and by radioactive phosphorus has been demonstrated. Although large doses of roentgen rays were employed in similar experiments, no inactivation of thiamin was apparent. These three types of radiation are all presumed to act through the common mechanism of ionization and hence qualitatively similar results would be expected from all. The difficulties of formulating any dosage comparisons for the three types of radiation have been pointed out and we cannot say that the roentgen-ray exposures fell within the same range of dosage used in the other experiments. Our results, therefore, might suggest but certainly do not prove that beta radiation has a qualitatively different effect from roentgen radiation on thiamin solutions *in vitro*.

The inactivation of thiamin by lead was noted but not further investigated. It is possible that this reaction deserves attention from those interested in heavy metal poisoning.

The chemical reactivity of thiamin as well as the nature of its degradation products is imperfectly known. Our results speak against one possible mechanism in the degradation of thiamin under the influence of radiation. Inactivation does not appear to proceed by splitting the molecule into thiazole and pyrimidine followed by selective destruction of either.

The animal experiments, although limited in scope, lend no support to the hypothesis that significant amounts of thiamin can be inactivated *in vivo* by therapeutic doses of radiation. The dose of roentgen radiation in these experiments was 800 r delivered to the whole body of mice, and the dose of P^{32} was 1.7 microcuries per gram of tissue. Both these doses are in excess of the therapeutic range for human beings. The fact that assays failed to reveal any decrease in the thiamin content of the blood and livers of the irradiated animals does not rule out the possibility that the absorption or utilization of thiamin might be impaired by irradiation *in vivo*.

In conclusion, we have failed to demonstrate the inactivation of thiamin by irradiation under any conditions which could be compared to clinical radiation therapy. However, thiamin is subject to inactivation by relatively large doses of radon or P^{32} administered *in vitro*.

SUMMARY

1. Exposure to radon and to radioactive phosphorus *in vitro* partially destroyed the activity of aqueous solutions of thiamin chloride as tested on *Phycomyces* and *Phytophthora*.

2. Large doses of roentgen rays produced no detectable effect.

3. Exposure of thiamin to large doses of radon did not result in splitting the molecule with subsequent selective destruction of either the thiazole or pyrimidine intermediate.

4. Heavy irradiation *in vivo* produced no detectable change in the thiamin content of mouse blood or liver.

We are indebted to Frederick Kavanaugh, Ph.D. for his assistance in reading the *Phytophthora* assays.

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ROENTGEN-RAY MEASUREMENTS UP TO 400 KILOVOLTS MADE WITH BERYLLIUM WINDOW TUBES*

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THE authors have previously discussed and presented data on this subject for voltages from 10 kilovolts to 250 kilovolts. The purpose of this paper is to extend the voltage range of the data up to 400 kv. The material included in this discussion is of interest because it makes available for the first time information dealing with the very softest components of a high voltage roentgen beam. These long wave lengths are absorbed by the glass wall of the conventional high voltage tube.

The inherent filtration of the roentgen-ray tube is always of interest to the radiologist. While it is true that a statement of the quality of the unfiltered roentgen beam expressed as the half-value layer might suffice in determining the biological factors involved, there may be factors that make desirable some means of evaluating the inherent filtration in terms of a commonly used filter material. The roentgen tubes (for use up to 200 kv. or 250 kv. at the very maximum) in use for many years had a thin glass wall and the tube was operated in air. In the past few years it has been necessary to increase the envelope thickness for higher voltage tubes. In some types of tubes the glass window through which the radiation emerges has been ground to a reduced thickness, the minimum thickness of this window being a function of the maximum voltage at which the tube is to be operated.

In addition to an increased wall thickness of the glass bulb, the tubes are usually enclosed in a protective housing of some kind. This housing may consist of a single dielectric such as bakelite. In the arrangement the inherent filtration consists of the glass wall of the tube plus the bakelite window of the housing. Even more recent is the trend to a tube housing consisting of a metal container filled with oil. The radiation window, usually of bakelite, is inserted in a wall of the metal housing. In this arrangement the inherent filtration consists of the glass wall of the tube, some oil, and the bakelite of the radiation window.

Another recent development is the so-called hooded anode type of tube for use at the higher voltages. In this type of tube the anode of the tube consists of a metal tube with the target at the end of this tube. The walls of the metal tube are quite thick and it is necessary to provide a window through the hollow anode directly below the focal spot of the tube. This is done by cutting a hole through the wall of the anode and covering the window with a thin sheet of some low absorption material through which the radiation emerges.

HIGH VOLTAGE ROENTGEN TUBE WITH BERYLLIUM WINDOW

In order to obtain the necessary low absorption, a special tube with a minimum inherent filtration was built. There are a number of materials which may be used in constructing such a tube. Lindemann glass was used by Behnken and Nitka.[2] Thoraeus[3] used a tube with an aluminun window 0.2 mm. thick. A window of this thin foil could be used but this type tube must be operated on a pumping system, a troublesome procedure at best.

The ideal window material is the metal beryllium, with an atomic number of only 4. A previous study[1] had led to the development of beryllium window sufficiently dense, pure, and homogeneous to be vacuum-tight. A tube had been constructed for low voltage work up to 250 kv. This

* Presented at the Annual Meeting of the Canadian Medical Association, Jasper Park, Alberta, Canada, June 15, 1942.

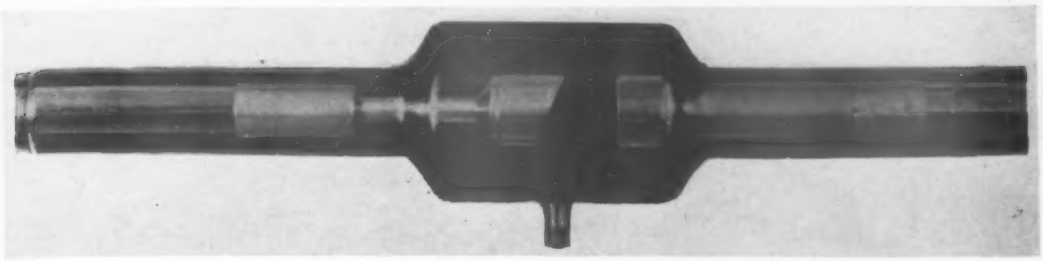

Fig. 1. Roentgen tube with low absorption window of 1.3 mm. pure beryllium.

tube was a standard 200 kv. tube with a beryllium window 1.3 mm. thick. Its construction is plainly shown in Figure 1. Some idea as to the absorption characteristics of beryllium may be had from Figure 2, in which absorption curves for beryllium are plotted for voltages from 10 to 50 kv.

For the present work a special tube that could be operated at 400 kv. was constructed. A vacuum-tight beryllium window was sealed on as an appendage to a standard 400 kv. hooded anode tube. The radiation window in the anode consisted of a beryllium disc. Since it seemed desirable to correlate the present data with the previous work, the thickness of the two windows was adjusted to give a total thickness of 1.3 mm. of beryllium. Figure 3 clearly shows the construction of the hooded anode 400 kv. tube.

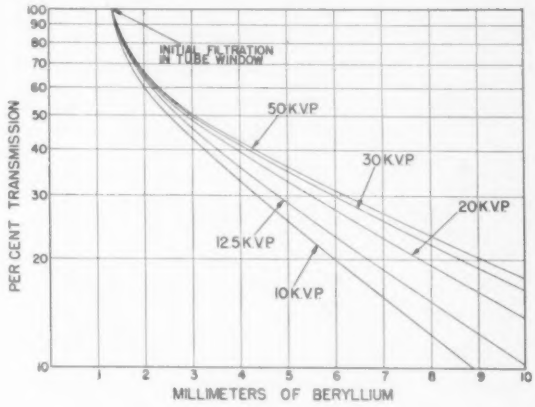

Fig. 2. Low voltage low initial absorption roentgen-ray transmission for beryllium.

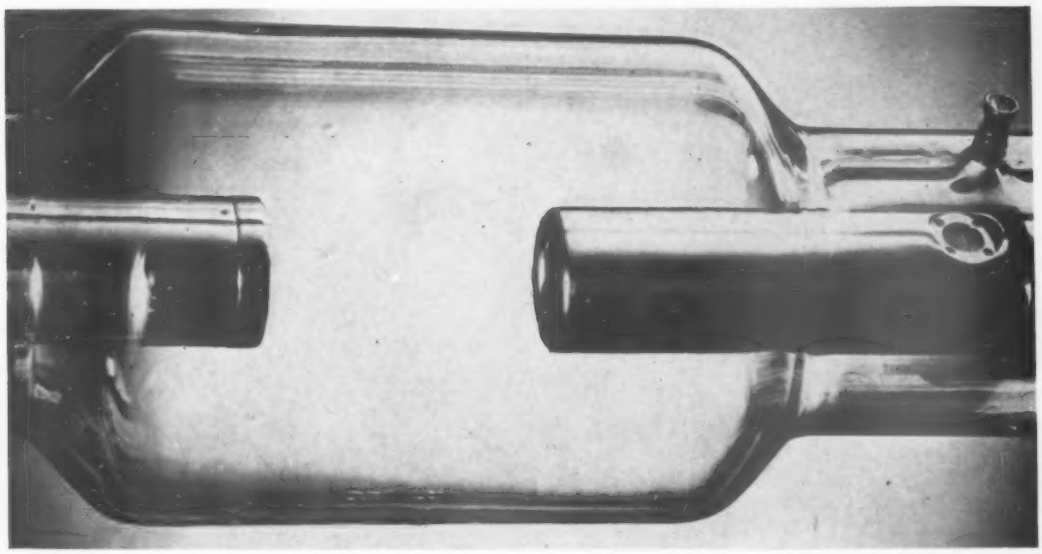

Fig. 3. High voltage roentgen tube with windows of pure beryllium totaling 1.3 mm.

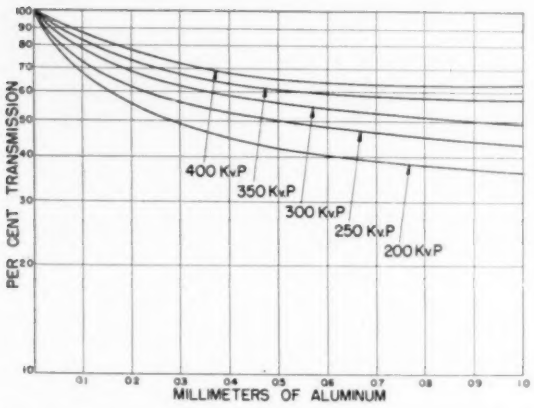

FIG. 4. Low initial absorption roentgen-ray transmission for 0 to 1 mm. aluminum.

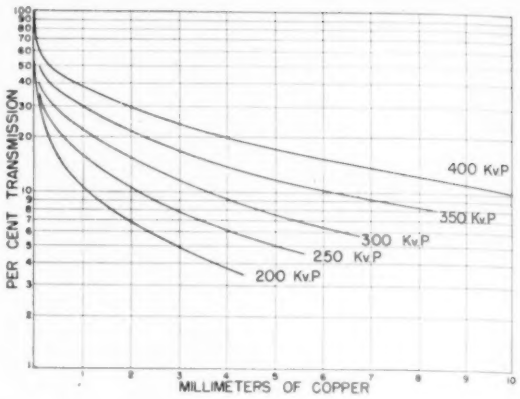

FIG. 7. Low initial absorption roentgen-ray transmission for 0.5 to 10 mm. copper.

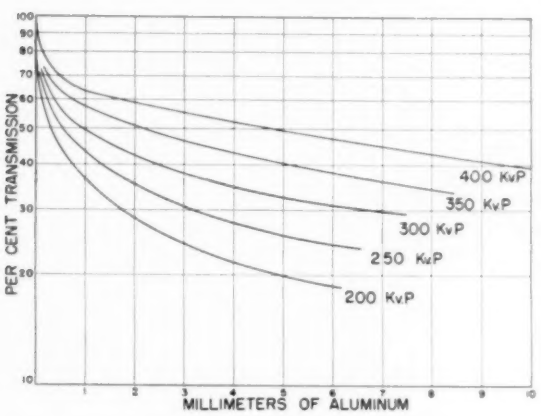

FIG. 5. Low initial absorption roentgen-ray transmission for 0.5 to 10 mm. aluminum.

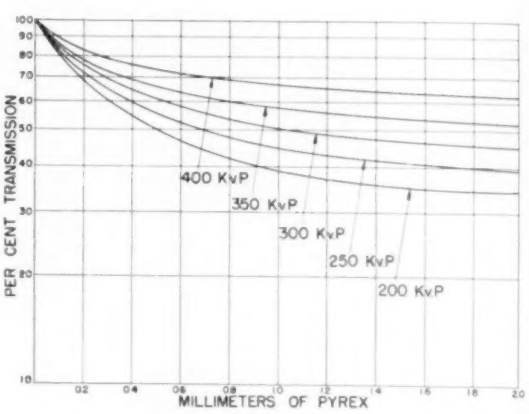

FIG. 8. Low initial absorption roentgen-ray transmission for 0 to 2.0 mm. pyrex.

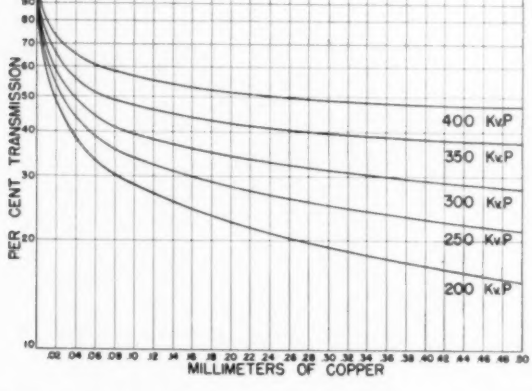

FIG. 6. Low initial absorption roentgen-ray transmission for 0 to 0.5 mm. copper.

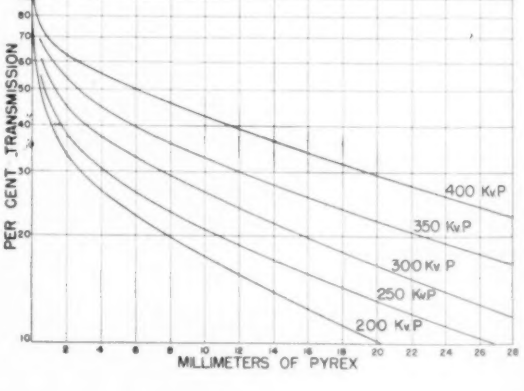

FIG. 9. Low initial absorption roentgen-ray transmission for 2 to 28 mm. pyrex.

The beryllium window in the envelope limited the field of coverage to 25 cm. diameter at a 100 cm. distance.

ENERGIZING CIRCUIT AND APPARATUS

The tube was energized by a Villard voltage-doubling circuit, which is quite comparable to the self-rectified circuits of this voltage most commonly used. It gives practically the same wave form with possibly 10 to 15 per cent more output per milliampere.

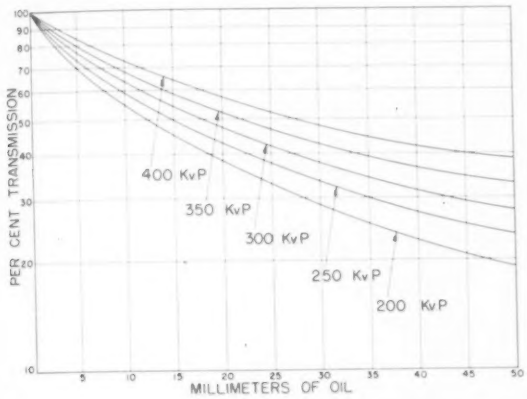

Fig. 10. Low initial absorption roentgen-ray transmission for 0 to 50 mm. transformer oil.

The voltage across the tube was measured with a sphere gap, using 25 cm. spheres. Tube current was measured by a pair of milliammeters, one in the low voltage circuit and one in the high voltage circuit.

The tube was operated in air in a lead-lined container. A double diaphragm system and a radiation shutter were provided for taking physical data.

ROENTGEN-RAY MEASUREMENTS

All roentgen measurements were made with a Victoreen, condenser type, thimble chamber. The focal chamber distance was 100 cm. and the tube current was 5 ma.

No part of the experimental set-up was disturbed during the work and no difficulty was encountered in reproducing data, although the work covered several weeks.

All the materials used in a high voltage tube and its housing were studied. Complete absorption data are presented for pyrex glass, transformer oil, bakelite, aluminum, and copper.

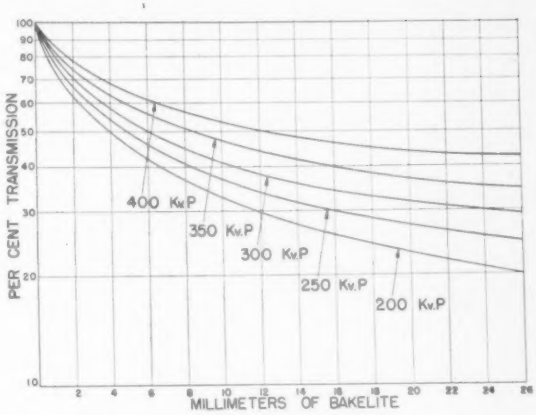

Fig. 11. Low initial absorption roentgen-ray transmission for 0 to 26 mm. bakelite.

Although previous work had covered the 200 to 250 kv. field, it seemed desirable to make complete studies from 200 to 400 kv. since this represents the useful therapy range of a hooded anode tube of the type used.

Complete absorption curves for the materials studied are found in Figures 4, 5, 6, 7, 8, 9, 10, and 11.

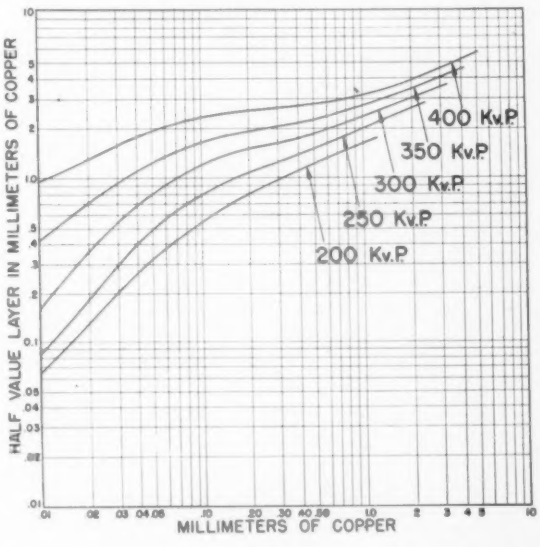

Fig. 12. Inherent filtration as a function of the half-value layer in copper.

DETERMINATION OF INHERENT FILTRATION

There are a number of ways in which the data obtained might be used to determine the inherent filtration.

Taylor and Singer[4] used a method of matching absorption curves. The method suggested by Thoraeus seems to be the one most easily used, since the only factor that must be known is the half-value layer expressed in millimeters of copper for the unfiltered beam at the voltage being used. By referring to Figure 12 the inherent filtration can instantly be determined. In the family of curves the half-value layer of the unfiltered beam has been plotted as the ordinate and the inherent filtration in millimeters of copper as the abscissa.

SUMMARY

1. A family of curves showing the relation of the half-value layer in copper to the inherent filtration at voltages from 200 to 400 kilovolts is presented.

2. Absorption data for pyrex glass, transformer oil, bakelite, aluminum, and copper for voltages from 200 to 400 kilovolts is shown.

3. A simple method for the determination of the inherent filtration for high voltage tubes is presented.

We hope it will be possible at a later date to extend the study to 1000 kilovolts by the construction of an experimental multisection, sealed-off tube with a wrought beryllium window for both reflected and transmission target studies.

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Vol. 50, No. 5

DOSAGE MEASUREMENTS IN CONTACT ROENTGEN THERAPY*

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DURING recent years, simultaneously with efforts to obtain roentgen rays at higher and higher voltages, for the delivery of greater depth doses, there has been a considerable development of the use of very soft radiation for the treatment of superficial lesions. Bucky[3] developed the "grenz-ray" tube, operating at 6 to 12 kv., and later 25 kv., which was of practical use only for lesions not more than about 1 mm. thick. Schaefer and Witte[19] employed cathode rays for the same purpose, and then modified their tube to produce roentgen rays, which they employed within body cavities. Chaoul and Adam[4] used apparatus very similar to theirs, and were also primarily interested in intracavitary irradiation.

These developments were, in part at least, made in a conscious effort to obtain a beam of roentgen rays which should be distributed within the tissues in the same manner as the rays from radium applicators; hence short distances were desired. This reached a limit in the Chaoul apparatus, in which the target actually forms the grounded end of the tube, so that distances of the order of a few millimeters are attainable, although in practice a few centimeters are usually employed. The beam of roentgen rays passes through the target, and hence is rather strongly filtered; according to Mayneord[13] it has a half-value layer of 3.3 mm. Al when the tube is operated at 60 kv. This is considerably harder than the radiation obtained with standard low voltage apparatus in common use in this country, which, operating at 100 kv. and without filter other than that inherent in the apparatus, gives radiation of a half-value layer of about 1.0 mm. Al. Hence any advantage of the Chaoul equipment lies not in the quality of the radiation but in the shape of the tube, which permits its ready insertion into body cavities, and in the short distances which can be used.

In an effort to obtain softer radiation, the Philips instrument was developed, with the filament as the grounded electrode close to the end of the tube, and the target set back a short distance and carrying the high potential. A roentgenogram of the tube (made with 1,000 kv. roentgen rays) is shown in Figure 1, together with a pinhole picture of the focal spot. The roentgen rays do not pass through the target, as in the Chaoul tube, and the inherent filter consists of a very thin glass window and a cap of organic material, having altogether, according to the manufacturers, a filtration equivalent to 0.2 mm. Al. The shortest distance obtainable, when the face of the tube is in contact with the skin, is the distance from the target to the external surface of the tube, specified by the manufacturers as 18 mm. The apparatus is ordinarily operated at 44 kv.

For the measurement of such soft roentgen rays, with very short target-chamber distances and high intensities, ordinary measuring instruments are inaccurate. The "air walls" of the standard Victoreen and similar thimble chambers, which are entirely satisfactory for measurements at 100 kv. or more, absorb an appreciable percentage of the 44 kv. radiation. Also, with a chamber having an inside diameter of even a few millimeters, at distances of the order of 2 cm. from the source of radiation, the distribution of ionization inside it is such that the reading cannot be specifically assigned to a definite distance. (This is the same difficulty as is encountered in the measurement of radium rays with thimble chambers at short distances.) Furthermore,

* Presented in part before the Forty-second Annual Meeting, American Roentgen Ray Society, Cincinnati, Ohio, Sept. 23–26, 1941.

the very high roentgen-ray output of this tube necessitates the use of special instruments for measurements at or near the contact position.

Lamerton[14] and Braestrup and Blatz[2] have published studies of the radiation from the Philips type of tube. In both cases these were made with special ionization chambers. Lamerton's were of "aerion"; the smallest had an internal diameter of 3 mm. His depth doses were measured in a water phantom. The chambers used by Braestrup and Blatz were of bakelite coated with carbon. They measured depth doses in both water and masonite pressdwood, finding slightly lower values with water.

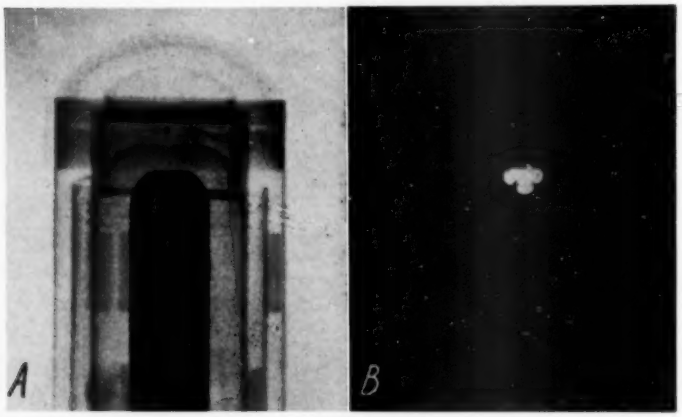


Fig. 1. *A*, roentgenogram of Philips contact therapy tube (made with 1000 kv. roentgen rays), and *B*, pinhole picture of focal spot. Actual size.

Measuring Apparatus. All measurements made by the authors just mentioned,[2,14] both in air and in phantoms, were made with closed chambers 3 mm. or more in internal diameter. For the measurement of the radiation in air, including both calibrations and absorption curves, it seems preferable to employ an open air chamber. For phantom measurements, it is desirable to use chambers less than 3 mm. in internal diameter to find out whether this makes a significant difference in the results obtained. Further, a study should be made of the suitability of "air wall" chambers for radiation of this quality.

Accordingly, two special types of chamber were employed in the present study. For investigations of the beam in air, including calibration, absorption measurements, and some tests of the inverse square law, an open air chamber was used, of the design shown in Figure 2*A*. The electrodes consist of three planes of silk threads, soaked in india ink to make them electrically conducting. The planes are about 1 cm. apart, and the threads in each plane a few millimeters apart. The two outer planes are charged to saturation potential, in this case about 200 volts; the inner plane, or collecting electrode, is connected to the special type of vacuum tube measuring instrument employed at Memorial Hospital.[8] Suitable guard rings are provided. Various limiting diaphragms can be inserted at the top of the chamber; the area of the diaphragm and the spacing between the electrodes being known, the ionized volume can be determined. The intensity of the beam can be measured in roentgens per minute if this device can be shown to fulfill the requirements of the definition of the unit. This can be tested by comparison with a standard instrument. This particular ionization chamber has been found to agree with the standard open air chamber from 60 kv. unfiltered to 200 kv. highly filtered (constant potential). For the present it is assumed therefore that it is also correct at 44 kv. This instrument is ordinarily called a "mesh chamber."

For measuring on or in the phantom, the extrapolation type of chamber, which has been so satisfactory for higher voltages[9,17]

should be particularly appropriate. Accordingly a very small one was constructed, as shown in Figure 2*B*. The lower plate is of lucite, 3.3 mm. thick and with further reinforcing as shown; the lead to the measuring instrument passes through it, as indicated. The entire lucite piece is coated with aquadag to make it electrically conducting; a very narrow scratch through the aquadag and into the lucite defines the collecting electrode and separates it from the outer conducting portion of the plate, the electrical capacity of the chamber as a parallel plate condenser. This capacity $C=A\epsilon/4\pi d$, where A is the area of the electrode, d the spacing, and ϵ the dielectric constant, which in the case of air (in the extrapolation chamber) is equal to unity. Hence $d=(A/4\pi)\times(1/C)$. Such a determination was made immediately preceding or following every ionization measurement with this chamber.

The data here reported were obtained with a standard Philips contact roentgen

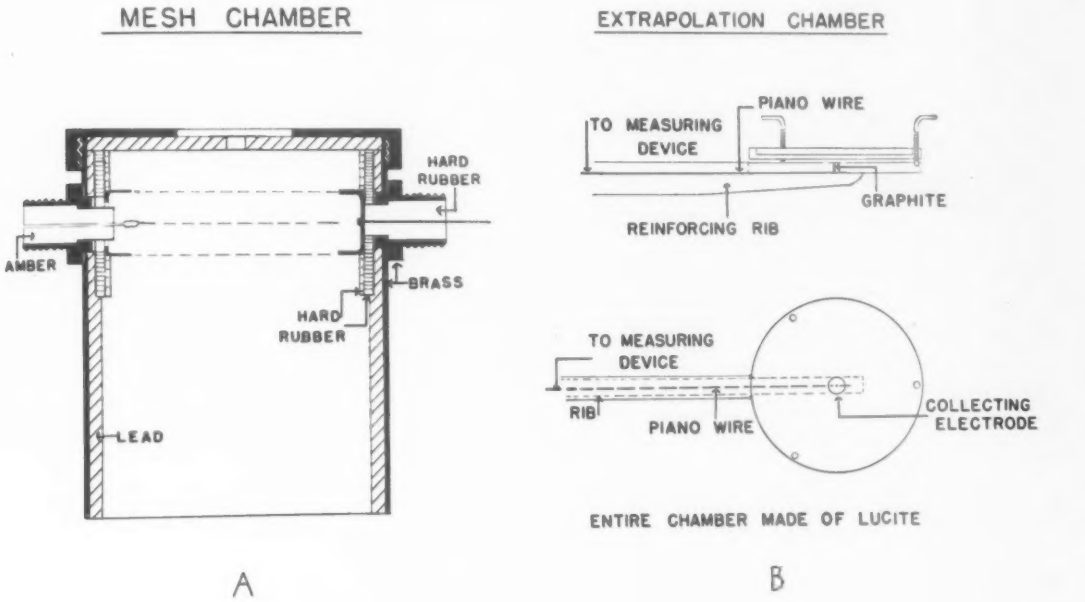


Fig. 2. *A*, open air chamber of mesh type, inside diameter 9 cm., height 13 cm. *B*, small extrapolation chamber, diameter of collecting electrode 4.96 mm. (For detailed descriptions, see text.)

which is grounded and serves as a guard ring. When a null method of measurement is employed, the scratch affords sufficient insulation. Two different upper electrodes were made, one a sturdy one of lucite 0.58 mm. thick, which is suitable for measurements within the pressdwood phantom, and one of cellophane 0.04 mm. thick, for surface measurements. The diameter of the collecting electrode is 4.96 mm.; the distance between the upper and lower electrodes can be varied from 0.15 mm. to several millimeters and can be accurately determined for each position by measuring

therapy unit, operated at conditions specified by the manufacturers. No direct determination was made of the voltage. Braestrup and Blatz[2] found by sphere gap measurements that under these conditions their unit operated at 44 kv.; they further checked this by means of a high resistance and a micro-ammeter. Lamerton[14] made Seemann spectrographs of the radiation emitted under the same conditions and found that the short wave length cut off occurred at 280 X.U., corresponding to 44 kv.

The tube was mounted on its regular

carriage in a vertical position. The supports for the various ionization chambers were carried on a table with a hydraulic device for adjusting its height. By means of a pointer attached to the chamber mount, and a scale fastened to the tube, it was possible to duplicate settings to a fraction of a millimeter.

Measurements in Air. With the mesh chamber diaphragm about 10 cm. from the face of the tube, the ionization current was measured for a series of diaphragms varying from 2.68 to 9.25 mm. in diameter. The ionization was proportional to the area of the diaphragm throughout the range, hence at this distance, within these limits, the size of the diaphragm is not important. This is the position used in making the absorption curves. For the contact position, the thickness of the diaphragm becomes an important factor. Since the source of roentgen rays is not a point, the available thick diaphragms do not properly define the beam. Accordingly one of silver 0.8 mm. thick and 5.02 mm. in diameter was constructed, and was used for all measurements at contact, or where the distance was varied. At 10 cm. distance, the reading with this diaphragm agreed with those with the lead diaphragms. Its lower face was considered the limiting part, hence the target-chamber distance was always 0.8 mm. greater than the distance from the target to the face of the tube, or of the filter, if one was used.

In this mesh chamber, the distance from the limiting diaphragm to the collecting electrode is about 3 cm. Since the radiation being studied is rather soft, the question may be raised as to whether it will undergo appreciable absorption in traversing this amount of air. It will be shown below that the half-value layer for the unfiltered beam is 0.3 mm. Al. For radiation of this quality, Siegbahn[20] gives the mass absorption coefficient in air as 1.53. In this case, the air in the ionization chamber would reduce the beam by less than 0.5 per cent, and the 13 cm. which was the greatest air path used in any measurements would only reduce the beam to 98 per cent of its value. Variations of 2 per cent in these measurements are close to the limit of experimental error. Hence for distances used in this study, absorption of the radiation in air is of no significance.

Since the source of radiation is not a point, but has a diameter of a few millimeters, the possibility of any divergence from the inverse square law must be investigated. With target-diaphragm distances from 1.8 cm. (contact with the end of the tube) to 15 cm., ionization readings were made with the silver diaphragm. For both unfiltered and filtered radiation, the inverse square law was followed from 2.5 to 15 cm., within the limits of experimental error. From 2.5 to 1.8 cm. the readings are lower than would be called for by the inverse square law, the discrepancy being 8 per cent at contact. This matter was further investigated with the extrapolation chamber, and will be discussed below.

TABLE I

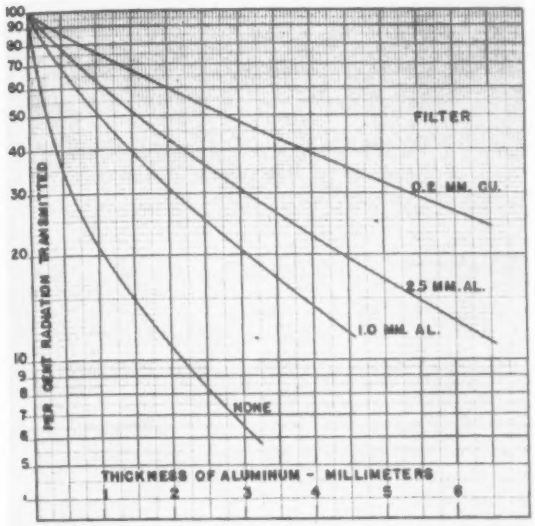
HALF-VALUE LAYERS FOR 44 KV. ROENTGEN RAYS

Filter	r Per Minute	Half-Value Layer	
		Aluminum mm.	Pressdwood cm.
0	11,800	0.3	0.5
1.0 mm. Al	2,600	1.6	1.7
2.5 mm. Al	1,020	1.6	2.2
0.25 mm. Cu	150	2.8	3.2
0.25 mm. Cu +1 mm. Al	115	3.2	3.4

Absorption curves for aluminum and pressdwood were made for the unfiltered beam and for the aluminum and copper filters provided with the apparatus. These are shown in Figure 3. Those for aluminum agree well with those previously published by Lamerton[14] and Braestrup and Blatz.[2] Curves for pressdwood have not been previously published. The half-values in aluminum and pressdwood for the various beams are given in Table 1, together with

the roentgens per minute at the contact position, as determined with the mesa chamber.*

Measurements with the Extrapolation Chamber. Before using the small extrapolation chamber to measure surface and depth doses, it is necessary to make certain fundamental tests of its suitability. First is the matter of spacing, or range of spacings to be employed. According to Gray,[10] and others,



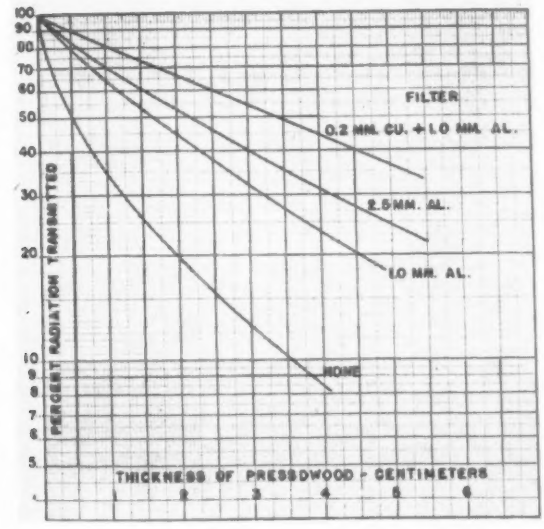


Fig. 3. Absorption curves of 44 kv. roentgen rays in aluminum and in pressdwood.

* These are larger than those obtained by other workers with closed chambers. The reason will be explained later in the paper.

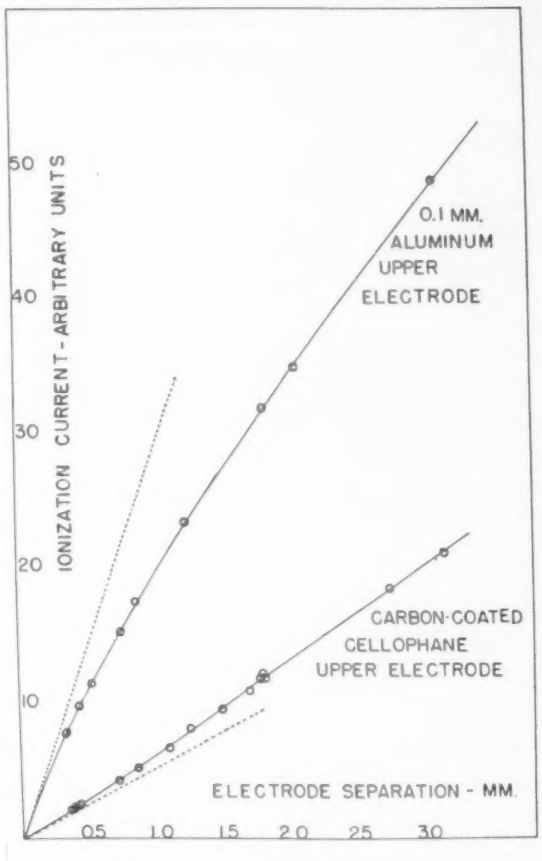

IONIZATION CURRENT - ARBITRARY UNITS
0.1 MM. ALUMINUM UPPER ELECTRODE
CARBON-COATED CELLOPHANE UPPER ELECTRODE
ELECTRODE SEPARATION - MM.

Fig. 4. Variation in ionization current with spacing, for carbon and aluminum electrodes.

if the chamber has no wall effect and measures correctly, the ionization is proportional to the volume, or, for such a chamber, to the spacing. That is, the increase in ionization per unit increase in spacing should be constant. This condition has been found to be fulfilled with other extrapolation chambers in the voltage range from 100 to 1,000 kv.[9,16,17] However for 44 kv., as employed in this tube, it was found not to be the case, For spacings from 0.2 to 1.2 mm. the ionization per unit volume increased somewhat more rapidly than the spacing. From this point on, the *rate* of increase was constant. The data are shown in the lower curve of Figure 4. The part for the first 1.5 mm. is not quite linear, but slightly concave downward. The part from 1.5 mm. on is linear. This behavior implies

the presence of some wall effect which must be investigated before the chamber can be employed for dosage or calibration measurements. No part of the variation can be attributed to changes in distance from the target to the center of the chamber with increase in spacing. With the lower electrode in a constant position, as the spacing is increased by raising the upper electrode,

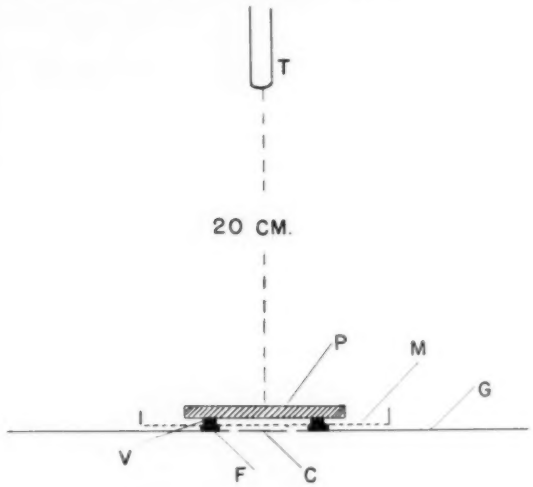


Fig. 5. Apparatus for investigating ionization by electrodes of different materials. *T*, Philips contact therapy tube; *G*, lower surface of large extrapolation chamber; *C*, collecting electrode; *F* and *V*, spacers; *M*, silk net electrode; *P*, small piece of pressdwood, coated on one side with aquadag and on the other with aluminum leaf.

of course the center of the chamber comes closer to the target. However, correction was made for this on the basis of the inverse square law. Since the target-chamber distance for these measurements was of the order of 12 cm., such corrections are valid, in view of the above mentioned test of the inverse square law with the mesh chamber, and of corroboration of this with the extrapolation chamber, to be discussed below. The ionization per unit volume increases by about 20 per cent from an electrode spacing of 0.2 mm. to one of 3.0 mm., as determined from the slopes of the curve at these two points. Therefore, the roentgens per minute as determined by this chamber depend on the electrode separation, becoming less, the smaller the spacing. The roentgens per minute determined for the 3 mm. spacing are 7 per cent less than that obtained for the same distance with the mesh chamber; for smaller spacings of course the discrepancy is greater. Similar results were obtained with filtered beams. Such differences would be expected if secondary electrons from the carbon coating of the electrodes contributed appreciably to the ionization. In regions where the effect of these electrons was predominant, the ionization would be less than where most of the ionizing electrons were secondaries from nitrogen or oxygen of the air.

In order to investigate the contribution of electrons from the electrode, the apparatus indicated in Figure 5 was employed. Instead of the small extrapolation chamber, a large one having a collecting electrode 3 cm. in diameter was used. Rings were cut from different thicknesses of the plastic material known as "vuepak"* with circular openings slightly larger than the collecting electrode. One of these rings rested on the lower plate of the chamber, and supported an upper electrode consisting of a fine silk net of rather coarse mesh (about 1 mm. openings) stretched taut on a frame and coated with india ink to make it electrically conducting. On this rested another vuepak ring on which could be placed the material whose secondary radiation into the collecting volume of the chamber was to be studied.

The first such radiator was a piece of pressdwood about 2 mm. thick, coated on one side with aquadag and on the other with aluminum leaf. A target-chamber distance of about 20 cm. was employed. With the radiator close to the tube, an ionization measurement was made. At this distance, no carbon or aluminum secondary electrons can reach the chamber. The radiator was then placed on the 0.27 mm. vuepak ring just over the chamber, and readings made with each face toward the collecting volume. As was to be expected, the reading with the aluminum side down was greater

* The authors are grateful to the Vuepak Company for liberal samples of graded thicknesses of this material.

than with the carbon down, the ratio being 240 to 100.

In order to investigate more closely the possible range of effect of carbon electrons, a series of readings was taken, with varying distances between the net electrode and the carbon face of the radiator, the separation between the net electrode and the collecting electrode of the ionization chamber being maintained at about 1 mm. For each position of the radiator, the effective ionized volume in the chamber was determined by the capacity method described above. It remained essentially constant throughout the experiment. The readings obtained are are shown in Table II. From these values it appears that the effect of radiation from the carbon continues to be significant to a distance of about 1.5 mm. (The actual range cannot be measured by such an experiment.)

Theoretically, the range in air of a carbon photoelectron of 40 kv. is about 2 cm. This, however, is assuming that it travels in a straight line; according to Terrill and Ulrey[21] its actual range is only about one-tenth of this. Furthermore, most of the photoelectrons are ejected at a large angle with the direction of the roentgen-ray beam. For 45 kv. in xenon the most probable angle is 82°; for carbon it would be slightly greater.[6] The length of the path in the forward direction is then proportional to the cosine of this angle, or, for 82° about 14 per cent of its path in the direction of its ejection. On the basis of either the observations of Terrill and Ulrey or Compton's calculations, it appears that a range of the order of 1.5 mm. is reasonable.

On this basis, the explanation of the curve for the cellophane electrode shown in Figure 4 would be as follows: The portion close to the origin, for small spacings, represents a condition where the ionization is almost entirely due to electrons from the carbon coating of the two electrodes, the plate separation being less than the range of these. The straight line for the latter part of the curve (wider spacings) represents the part where added ionization with increased spacing is due entirely to electrons from the air.

If this is true, it follows that after the electrode separation is increased beyond the range of the carbon electrons for either electrode, the *increment* of ionization per unit increment of volume should agree with the ionization per unit volume measured in the open air mesh chamber discussed in the first section of this paper. This was tested by determining the increment in ionization per unit increment in volume for electrode separations above 2 mm. (which is seen to be past the part of the curve where carbon electrons may be significant), and by comparing this with the ionization per unit volume determined by the mesh chamber at the same distance. A target-chamber distance of about 10 cm. was employed, the effective distance being considered to the middle of the extrapolation chamber, and to the bottom of the limiting (silver) diaphragm of the mesh chamber. Corrections for small differences in distance (never more than a few millimeters) were made on the basis of the inverse square law. Under these conditions, using the unfiltered beam, the ionization per cubic centimeter for the *increment* of volume in the extrapolation chamber agreed within experimental limits with that obtained in the mesh chamber.

Table II

MEASUREMENTS TO DETERMINE EFFECTIVE RANGE OF CARBON ELECTRONS

Spacing between Carbon Coating and Upper Mesh mm.	Ionization (arbitrary units)	Electrode Spacing Inside Chamber mm.
0.27	10.2	1.11
0.41	11.7	1.12
0.57	13.1	1.12
1.14	17.2	1.10
1.71	20.1	1.10
300.0	20.0	1.10

From the preceding analysis it appears that for calibration in terms of roentgens of x-ray beams whose energy is preponder-

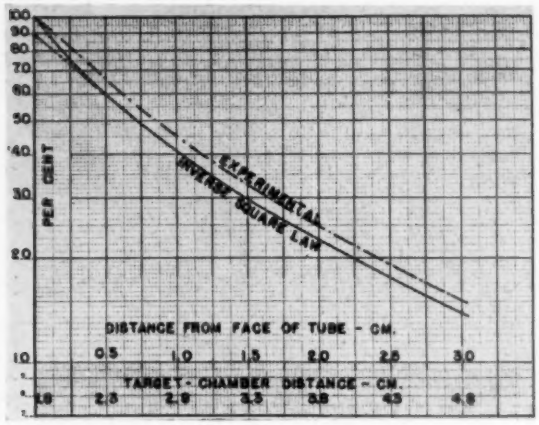

PER CENT
EXPERIMENTAL
INVERSE SQUARE LAW
DISTANCE FROM FACE OF TUBE - CM.
0.5 1.0 1.5 2.0 2.5 3.0
TARGET - CHAMBER DISTANCE - CM.
2.3 2.8 3.3 3.8 4.3 4.8

Fig. 6. Curve showing variation of ionization with distance.

antly in this long wave length region, the small closed chamber customarily employed, in which electrical conductivity depends on a carbon coating, is not satisfactory. The ionization registered by it is too small, the amount of divergence from the correct value depending on the geometry of the chamber and on the quality of the radiation being measured. This brings out the importance of calibrating against a standard chamber for a range of qualities including the one to be measured.

The fact that the extrapolation (or any other carbon-lined chamber) is not satisfactory for measurement of this radiation in roentgens does not necessarily mean that it cannot be employed for obtaining *relative* back scatter and depth doses, if the spacing is kept constant. If the quality of the beam does not change very much within the region of depths investigated, the same percentage of air and carbon electrons register at all depths, and the relative values are correct. On the other hand, if the quality does change considerably, the distribution between air and carbon electrons changes, and the relative ionization with increasing depth is either too low or too high, depending on whether the radiation becomes softer or harder. Ordinarily it is expected that radiation becomes softer within the phantom, because of the increasing contribution of the scattered rays. However, with the quality under consideration, and especially with the small fields employed, the small scatter, and the increasing filtration effect of the pressdwood of the phantom, the result may be hardening rather than softening the beam, or the two effects may essentially counteract each other.

If the change in quality is appreciable, relative depth doses determined with quite different spacings in the extrapolation chamber should be different, since the relation between air and carbon electrons is different for the two. Accordingly, surface and depth dose measurements were made for the unfiltered beam, with a 2.0 cm. cone, contact position (1.8 cm. target-phantom distance), and electrode spacings of 0.6 and 1.65 mm. These particular spacings were selected because it was desired to have the smaller within the carbon-controlled region (Fig. 4) and the larger within the air-controlled region, and these particular spacers were available. When the data thus obtained were corrected for the difference in distance to the centers of the two chambers, on the basis of data shown in Figure 6 (see below) the relative depth doses were the same, within the limits of experimental error. Hence it appears that the change of quality as the beam passes into 3 cm. of pressdwood is unimportant. (It is of no practical interest to carry measurements to greater depths.) Therefore it appears that the extrapolation chamber, with spacing as small as desirable, is satisfactory for determining percentage depth doses for unfiltered radiation of this quality. It is also assumed that it is satisfactory for determining percentage depth doses for filtered radiation at this voltage.

Inverse Square Law. It has been stated above that with the mesh chamber the inverse square law was found to be followed for target-diaphragm distances from 2.5 to 15 cm. A similar study was made with the extrapolation chamber with a small spacing, particular attention being paid to the region close to the tube. The results are shown in Figure 6. The solid curve indi-

cates percentage decrease according to the inverse square law, from 1.8 cm. target-chamber distance (contact for the unfiltered beam) to 5.0 cm. (3.2 cm. from face of tube). The (upper) broken line indicates the experimentally determined decrease. If the experimental curve were superimposed on the theoretical one, the dotted lower curve would indicate the divergence. In other words, the experimental data follow the inverse square law after a distance of 0.5 cm. from the face of the tube while for the shorter distances the decreases are not so great as the law would call for. This is to be expected since the focal spot is not a point. Similar curves were obtained for filtered beams.

Back Scatter. From an earlier study of back scatter[16] it would be expected that such scatter for the present qualities of radiation and field sizes would be small. Its actual measurement is complicated by the wall effect of the extrapolation chamber. It is possible to determine with this chamber readings without and with the phantom. If the chamber itself introduces no scattered radiation, the ratio of these values should be the back scatter. However, because the lower electrode is 3.3 mm. thick, it contributes some scatter to the reading with no phantom; indeed further phantom material, for unfiltered radiation and the contact position, increases the reading by only 1 or 2 per cent. On the other hand, to obtain the air reading with the mesh chamber and the phantom reading with the extrapolation chamber necessitates correcting the latter for the carbon effect. This requires making a series of readings for different spacings, at contact position, and the correction may finally introduce a greater error than arises from neglect of the lower electrode. Since the back scatter is small in any case, small errors in it are not of practical significance and a thorough investigation of it with the present set-up was not deemed warranted.

Depth Doses. Percentage depth doses were measured in a pressdwood phantom*

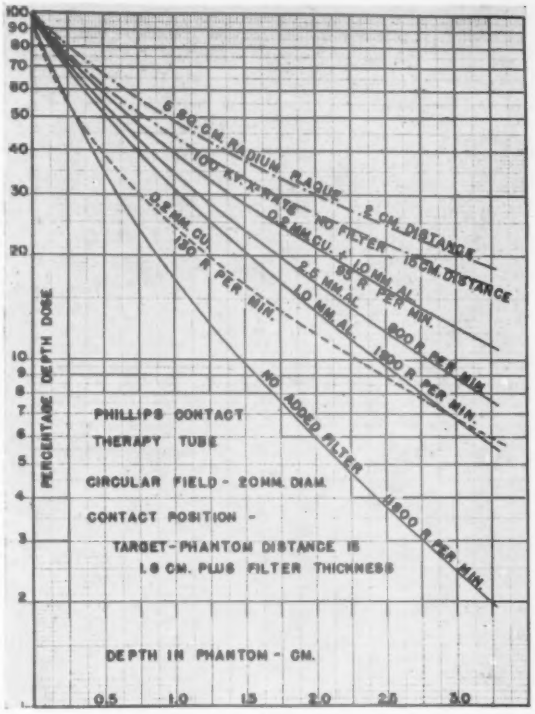


FIG. 7. Curves showing percentage depth doses for unfiltered and filtered 44 kv. roentgen rays.

for all filters, all cones and all distance spacers supplied with the machine. In Figure 7 are given the results for the 2.0 cm. cone, for the various filters, all at contact distance.† The roentgens per minute for each beam as determined by the mesh chamber (without back scatter) are indicated on the figure. For comparison, curves are also given for a small radium plaque at 2 cm. distance‡ (the same distance as the filtered roentgen rays) and for 100 kv. roentgen rays unfiltered, at 15 cm. distance.

The effect of the size of field on depth dose is shown in Figure 8 for unfiltered radiation at contact position (1.8 cm. target-phantom distance). The effect of increasing target-skin distance is shown in Figure 9,

* There is some question as to whether pressdwood is a satisfactory tissue substitute for radiation at this voltage. Braestrup and Blatz[2] state that measurements in a water phantom gave slightly lower values. However differences greater than 10 per cent in values at 2 cm. depth are not to be anticipated and such variations are not of clinical significance for radiation of this quality.

† Since the contact distance depends on the amount of filter interposed between the tube and the skin, it is different for each filter. Target-skin distances are indicated on the curves.

‡ Calculated from Paterson and Parker curves.[15]

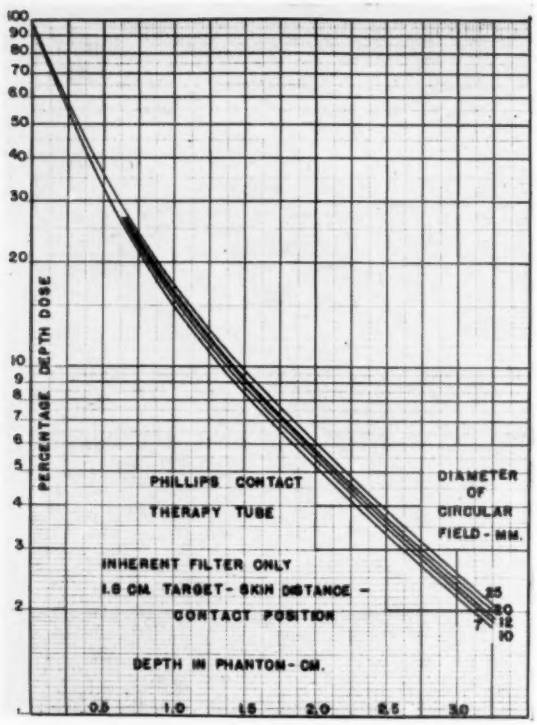


Fig. 8. Curves showing variation in depth dose with variation in size of field.

for unfiltered radiation and the 2.0 cm. cone. The radium plaque and the 100 kv. unfiltered beam are again included for comparison. For filtered beams the increases will be in the same ratios.

The relative increase in depth dose with increase in distance as experimentally determined agrees with that calculated on the basis of the inverse square law, as corrected in accordance with Figure 6. Hence the depth doses for any reasonable distance can be calculated from the data for contact, for the same field and filter, if the proper correction is made for short distances. This can be done either by reading all distance factors for the contact position from the curve of Figure 6, or by calculating the factor for the 0.5 cm. depth in the usual manner, increasing it by 8 per cent, and then calculating for all other depths from this point instead of from the surface, using only the inverse square formula. It is convenient to have a table for reference instead of making such calculations each time. This is given in Table III for the target-skin distances of 3.4 and 4.5 cm. provided by the extension cones supplied with the apparatus. The reason for the reversal with the additional distance, so that the factor is first greater and then less than for the corresponding distance with no filter is found in the shape of the curve of Figure 6.

Calculation of Depth Doses from Absorption and Inverse Square Data. Since with this type of tube the fields are small and the scatter relatively unimportant, it is possible to calculate depth doses quite satisfactorily on the basis of the pressdwood absorption curves and the inverse square law as modified according to Figure 6. To a depth of 2 cm. the calculated values do not vary from the measured ones for small fields by more than 4 per cent. For larger fields the variation will be somewhat greater because of scatter.

Protection. There has been some tendency to disregard the need of protection

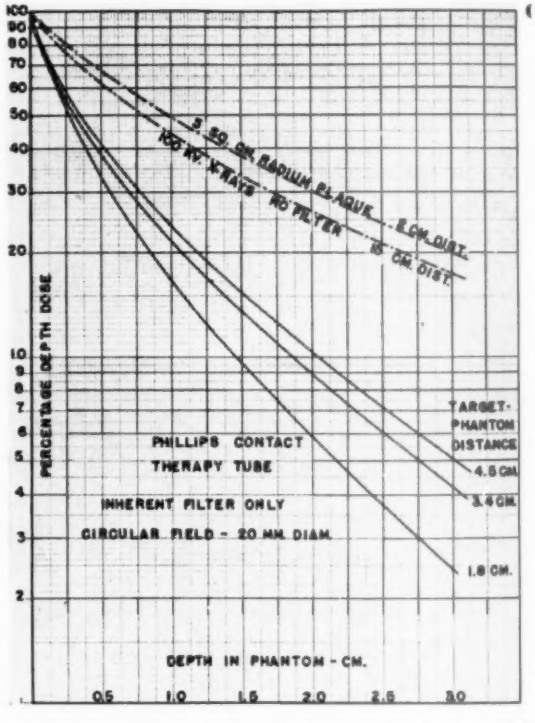


Fig. 9. Curves showing variation in depth dose with target-phantom distance.

with this apparatus. Because of the short irradiation times, and the unpenetrating nature of the radiation, little attention has been given to shielding the operator.

With the tube end in contact with a pressdwood phantom 30 cm. in diameter, no limiting cone, and no filter, measurements were made with a spherical celluloid ionization chamber having a wall thickness of about 1 mm. and a volume of 128 cc. The results are shown in the diagram of Figure 10, the values being corrected for absorption of radiation in the wall of the ionization chamber. It is evident that an operator holding the tube or standing close to it receives a day's tolerance dose in a very short time.

With a standard fluoroscopic apron interposed between the tube and the ionization chamber, the intensity at point *A* was reduced to 0.0004 r per minute, which is well within safe limits for a considerable number of treatments daily. This same apron reduced the intensity of the direct unfiltered beam to about 0.1 per cent of its original value.

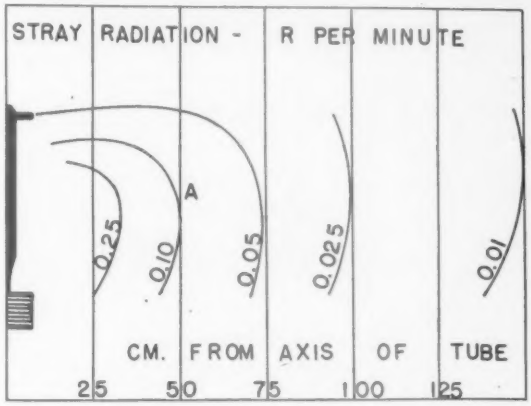


Fig. 10. Curves showing stray radiation in roentgens per minute around Philips contact therapy tube operated at 44 kv., 3 ma., end of tube in contact with pressdwood phantom.

When a cap of $\frac{1}{8}$ inch lead was slipped over the end of the tube, extending to a distance about 4 inches behind the target, the stray radiation at point *A* was reduced to about 0.02 per cent of its original amount.

In order to simulate cavity irradiation, the end of the tube was again placed in contact with the phantom, and the tube for a distance of 8 cm. back from the contact end surrounded with 5 cm. of wood. Under these conditions the radiation at point *A* was about half as great as with no wood around the end of the tube. When the 5 cm. of wood was increased to 12 cm. on the side toward the ionization chamber, the reading at this point was reduced to about 10 per cent of its original value, that is, to 0.01 r per minute. It is evident that it cannot be taken for granted that in cavity irradiation there is no appreciable stray radiation.

Since the lead rubber fluoroscopic apron affords essentially complete protection to the covered part of the body, the practice should be insisted upon of the operator *always* wearing it. Even so, the face and arms are exposed. The tube should never be held by the operator while a treatment is being

Table III

Factors for calculating percentage depth doses for extension cones (applicable to all fields)

Depth cm.	Factor by which Percentage Depth Dose for Contact Position Must Be Multiplied to Obtain Dose for Same Depth with Extension Cone					
	Extension cone increasing all distances by 1.6 cm.			Extension cone increasing all distances by 2.7 cm.		
	Filter			Filter		
	0	1 mm. Al	2.5 mm. Al	0	1 mm. Al	2.5 mm. Al
0	1.00	1.00	1.00	1.00	1.00	1.00
0.25	1.05	1.06	1.07	1.09	1.11	1.13
0.5	1.15	1.16	1.17	1.23	1.24	1.24
0.75	1.25	1.24	1.24	1.36	1.36	1.36
1.0	1.34	1.32	1.31	1.50	1.48	1.45
1.5	1.51	1.46	1.42	1.70	1.68	1.65
2.0	1.63	1.58	1.54	1.92	1.88	1.84
2.5	1.75	1.68	1.61	2.22	2.11	2.00
3.0	1.88	1.79	1.70	2.30	2.25	2.20

administered, but supported rigidly by some mechanical arrangement. The new stand furnished by the manufacturers is satisfactory. The tube should be as far from the controls as possible in every case. Whenever practicable the patient should be placed so that the target end of the tube is below the level of the top of the case containing the transformer, so that this is interposed between the target end of the tube and the operator. The operator, standing behind the controls, will then be at least a meter away and shielded from radiation scattered directly from the patient. Under these circumstances he is probably safe in administering several treatments daily. However, if the instrument is used extensively, it is desirable to provide a protective screen for the technician.

Theoretical Considerations Regarding Results of Ionization Measurements. It has been mentioned that the ionization per unit volume increases with increased spacing in the extrapolation chamber, and considerations have been brought forward to indicate that this is due to the influence of secondary electrons emitted from the carbon coating of the electrodes. It is of interest to investigate this matter from a theoretical point of view, and see whether the application of accepted formulae for absorption will quantitatively express the variations found.

To obtain further information for this purpose, an upper electrode was made of thin aluminum foil (about 0.1 mm.) and determinations of ionization with increasing spacing made as with the thin cellophane electrode described earlier. The results, corrected for true absorption of the primary beam in the aluminum electrode, are plotted in the upper curve in Figure 4. For close spacing, the electrons from the aluminum predominate. They do not, however, form the entire ionization, because the carbon-coated lower electrode still makes its contribution. Since the aluminum electrons are more numerous, the ionization readings in the region where they are effective are greater than when the ionization is mainly due to electrons from the air. Hence the first part of the curve is concave downward. After the spacing exceeds the range of the Al and C electrons, and the increment in ionization with increment in spacing is due to air, the line tends to become straight, as in the case of two carbon electrodes.

When the spacing is extremely small, essentially the entire ionization is the result of secondary electrons emitted from the faces of the electrodes as the result of either photoelectric or Compton absorption of roentgen rays at or very close to the surface of the electrode material. The ratio of the slopes of the two curves at the origin (zero spacing) is the ratio of the ionizations at the lower limit of separation. It should be the ratio of the energies of the electrons resulting from the roentgen-ray absorption just mentioned.

If E_λ represents the energy for any particular wave length λ of the primary roentgen-ray beam the energy converted into ionization per electron of the wall material is represented by $E_\lambda(1-e^{-(\tau+\sigma_a)})$ where τ and σ_a are the *electronic* photoelectric and scattering coefficients respectively for the λ in question. Since $(\tau+\sigma_a)$ is very small this expression reduces to $(\tau+\sigma_a)E_\lambda$. Something proportional to the maximum energy available for the production of ionization would be obtained by summing up such terms throughout the actual wave length range employed.

A theoretical evaluation of this summation can be obtained by the aid of a formula developed by Kramers[12] together with the accepted formulae for τ and σ_a and by published tables of complete absorption coefficients. Kramers' formula expresses the energy distribution in the continuous spectrum and has been found to give results in good agreement with experiment in the region below 110 kv. It is

$$I_\nu = \frac{s\times 8\pi\times e^2h}{3\sqrt{3}AC^3m} Z(\nu_0-\nu.)d\nu.$$

where ν_0 = highest roentgen-ray frequency present,

s = number of electrons striking target in unit time,
Z = atomic number of material of target,
A = a constant numerical factor (approximately 6),
e = electronic charge,
m = electronic mass,
h = Planck's constant,
c = velocity of light.

For any particular target material and filament current, the relation can be rewritten in the form

$$I_\lambda \propto \frac{1}{\lambda^2}\left(\frac{1}{\lambda_0}-\frac{1}{\lambda}\right)d\lambda$$

or, in terms of voltage

$$I_\lambda \propto V^2(V_0-V)d\lambda$$

where V_0 is the maximum voltage applied to the roentgen tube, and V the voltage corresponding to the wave length λ, according to the well known relation $V=12.354/\lambda$, V being in kilovolts and λ in Ångströms.

By means of this formula, the spectral distribution of the energy emitted from a target with a peak voltage of 45 kv. was calculated. The manufacturers state that the tube employed in the experimental work has an inherent filter equivalent to 0.2 mm. Al. The cellophane electrode has no appreciable absorption, hence the beam effective in the chamber after traversing it is essentially the same as that escaping from the tube. The aluminum electrode, of course, reduces the intensity of the beam. The absorption coefficients given by various authorities[1,6,7,22] for the various wave lengths in the beam were applied to the calculated spectral curve to reduce the intensities by the 0.2 mm. Al inherent, and by the 0.1 mm. Al additional filters. The spectral curves thus obtained are given in Figure 11*A*. The energies for the various wave lengths according to these curves are the ones which are acted upon by the above mentioned coefficients τ and σ_a.

It would be possible to calculate τ from the formula[11]

$$\tau_{\text{atomic}} = KZ^p\lambda_q$$

and σ_a from the Klein-Nishina formula.[18] A simpler approach is to make use of the tabulated experimental values for μ, the total absorption coefficient, for the various wave lengths, and the fact that

$$\tau+\sigma_a=\mu-\sigma_s$$

and calculate only σ_s, the scattering coefficient, using the Klein-Nishina formula. This is also preferable in view of the fact that values for the constants in the expression for τ are not as definitely known as might be desired.

Accordingly values of σ_s were calculated for a range of wave lengths covering the curves of Figure 11*A*. Values for μ/ρ for carbon and for aluminum from various sources[1,6,7,22] were collected and plotted so that the absorption coefficients for the chosen wave lengths could be read. Since the σs are electronic, and the μs are per gram, it is necessary to divide the latter by the numbers of electrons per gram for carbon and aluminum respectively to obtain the desired electronic coefficients.

For the chosen wave lengths, $E_\lambda(\tau+\sigma_a)$ was calculated for the two electrodes, by multiplying the appropriate value from the correct curve in Figure 11*A* by the calculated absorption factors. From these results were plotted the curves of Figure 11*B*. The areas under these curves should be proportional to the energy expended in producing ionization in chambers of aluminum and carbon respectively, provided that the energy of *all* of the electrons resulting from these absorption acts was completely used in ionization. Actually, of course, some of these electrons are absorbed wholly or partly in the electrode material, but compensation is afforded by the underlying layers. There is no way of estimating the actual fraction thus lost, and it may differ for the two materials, but probably only slightly.[10] Therefore, the ratio between the areas under the curves should afford a reasonable approximation to the ratios of the ionization currents in ionization chambers with carbon and with aluminum walls, when the

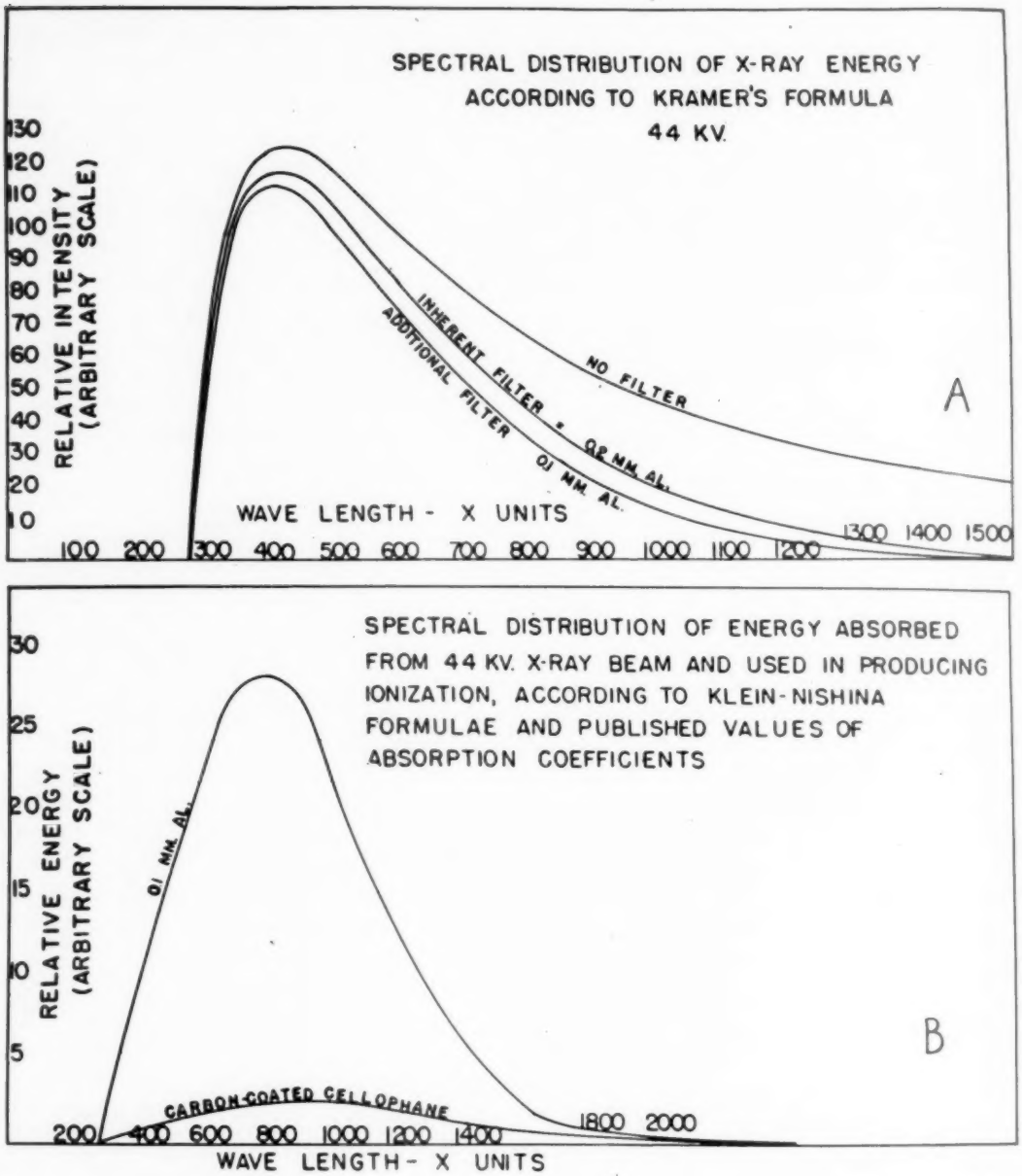


FIG. 11. *A*, theoretical spectral distribution of intensity for 44 kv. roentgen rays. *B*, theoretical spectral distribution of energy producing ionization in extrapolation chamber at vanishingly small spacing.

spacing between the electrodes is vanishingly small.

These areas were measured with a planimeter; their ratio is 8.3.

Returning to Figure 4, the slopes of the curves for the cellophane and aluminum electrodes are the slopes of tangents drawn to them at the origin. These can be constructed to a fair degree of accuracy as shown by the dotted lines; their ratio is 5.2.

This is quite different from 8.3. However it must be remembered that in the actual chamber, only one electrode was aluminum; the carbon remained effective for the other. In the wave length range under considera-

tion, most of the ionizing electrons are the result of photoelectric absorption, and of these, essentially equal portions are emitted backward and forward of a plane at 90° to the direction of the primary roentgen-ray beam.[6] Hence it is not far wrong to assume that in the all-carbon chamber half the ionization results from electrons emitted from either electrode. Since the lower carbon one acts with the upper aluminum one, the ratio 5.2 represents the ratio of ionization in a chamber half aluminum and half carbon to that in one entirely carbon, other things being equal. If the ionization in the all-carbon chamber be considered as unity, that due to each electrode is 0.5. If that in an all-aluminum chamber be represented by A, then

$$5.2-0.5=\frac{A}{2}, \text{ or}$$

$$A=9.4.$$

Since the all-carbon chamber has been set as unity, the ratio between all-aluminum and all-carbon is 9.4. This is 13 per cent more than the theoretical value of 8.3. Better agreement than this could not be hoped for, in view of the empiric nature of the formula from which the spectral curves were computed, and of the other approximations which have been made. It appears evident, on the basis of these calculations, that the differences in the readings of the carbon and aluminum chambers can be completely accounted for by differences in secondary radiation from the electrodes.

SUMMARY

Two ionization chambers especially adapted for the study of low voltage roentgen rays are described: one for the measurement of the beam in air, the other for determination of relative surface and depth doses.

Absorption curves for aluminum and for pressdwood, made with the "mesh chamber," are given for 44 kv. roentgen rays.

The matter of the measurement of these rays with small carbon-lined chambers is investigated; it is concluded that such chambers are not suitable for measurement in roentgens of x-ray beams in this voltage region. With certain precautions, they can be used to obtain relative surface and depth doses within the limits of accuracy required in clinical work.

Percentage depth dose data for filtered and unfiltered beams, for various fields and distances were obtained with a pressdwood phantom; they are presented in curves and tables.

The distribution of stray radiation around the tube is shown diagrammatically. The standard lead rubber fluoroscopic apron is found to afford satisfactory protection from these rays.

A theoretical analysis has been made of the radiation produced at 45 kv. (peak) and of the portion of this which is absorbed and results in the measured ionization. The results are found to be in reasonably good agreement with the experimental data.

Acknowledgments. The authors wish to express their gratitude to Dr. G. Failla, who designed the special ionization chambers, for his help and interest throughout the course of the work. They are also much indebted to Mr. L. D. Marinelli for the calibration of the mesh chamber, and for the suggestion of the analytical study of the radiation and of the methods of carrying it out.

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Vol. 50, No. 5

DEPTH DOSE MEASUREMENTS IN CONTACT ROENTGEN THERAPY ON A BIOLOGICAL TEST OBJECT (RABBIT'S SKIN)*

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IN CONTACT roentgen therapy, only small volumes of tissue receive significant amounts of radiation; yet the knowledge of depth dose distribution is just as important here as in deep roentgen therapy. Measurements of depth dose distribution in contact therapy have been made by several authors.

Depth dose curves collected from four papers[1,2,7,10] have been condensed in Figure 1. The measurements have been taken under almost identical conditions: Philips "Contax" apparatus; 50 kv. (peak) and 2 ma.; no filter, contact distance (18–20 mm.), round portal area of a diameter from 11 to 12 mm.; phantom material: water, pressdwood, or paraffin. Three curves are based on direct ionometric measurements. Braestrup and Blatz[1] used a thimble chamber of 4 mm. diameter, Lamerton[7] a shallow cylindrical chamber of 2.5 mm. depth, Quimby and Focht[10] an extrapolation chamber of 0.5 mm. depth. These three curves are fairly similar to each other, yet their differences are too large to be negligible. den Hoed[2] calculated his curve from

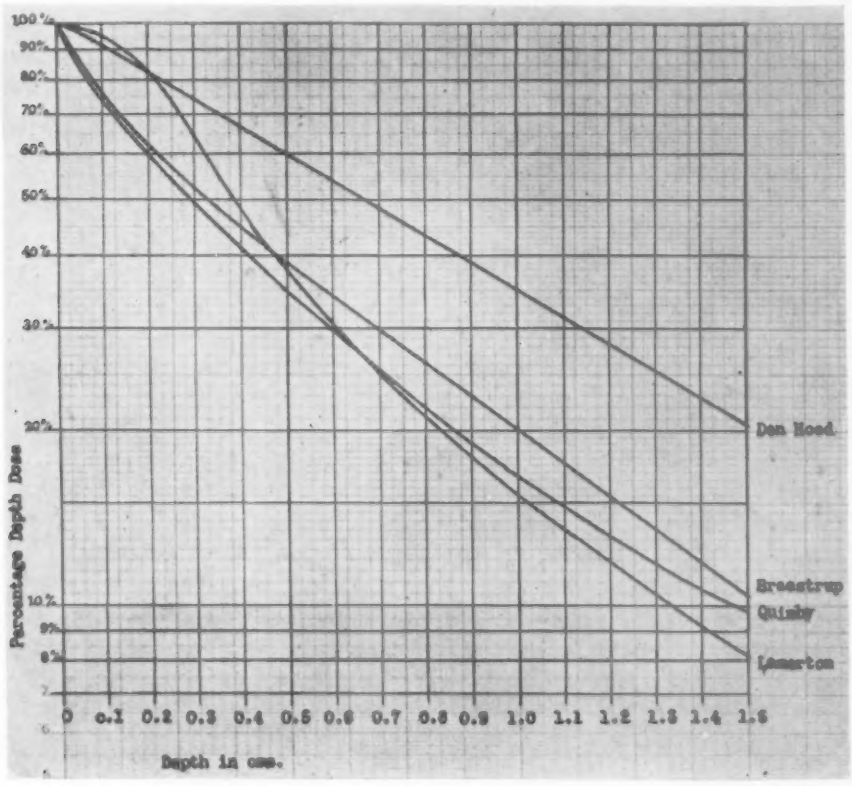

FIG. 1. Depth dose curves for contact therapy. All curves are stated to apply to the following conditions: Contax apparatus, contact distance, no additional filter, field 11–12 mm. diameter.

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dosage measurements in air obtained by means of Holzknecht pastilles, and an ionometric paraffin absorption curve. His results deviate widely from those of other authors.

Not knowing which curves to rely upon, we thought it interesting to ascertain what actually happens to a biological object at different depth levels. Methods of depth dose estimation based on biological tests have been worked out and have been used for several years.[6,8] Depth dose distributions as established by bio-assay are not necessarily identical with the r dose distribution. Different living objects react differently to changes of dosage, dosage rate and quality, with the result that "biological" depth dose curves may differ from each other[4] and from the "physical" ones. Yet, if the results of well controlled biological tests differ significantly from the physical findings and this difference cannot be explained either by the type of dose-response relation of the test object, or by faulty arrangement for the irradiations, it is probable that the technical set-up of the physical measurements will prove to be imperfect.[8]

Table I

Example of an experiment

Control fields: 12,000, 15,100, 19,100, 24,000 r				
Test fields	Thickness of wax block in millimeters	0.33	4.0	10.0
	Dose in roentgens	27,700	40,000	80,000
Range of control doses in percentage of the test doses		45–90%	30–60%	15–30%

The biological test object used in this study was the skin of the rabbit's ear. Depth dose estimates were established by comparing reactions to doses delivered directly with those given through layers of absorbent of known thickness.

Experimental procedure

The apparatus used was the Philips "Contax." Its working conditions are stated to be 50 kv. (peak), 2 ma., 2 cm. target distance (with localizer); inherent filter equivalent to 0.2 mm. Al.[2,4] Irradiations were given without additional filter. A localizer cone of brass with a circular opening of 12 mm. diameter was used. The output of the tube was measured with a small thimble chamber at 5 cm. distance, the doses at contact distance estimated assuming validity of the inverse square law. This is not quite correct. It causes a certain error in the determination of the absolute doses, which, however, does not influence the estimation of relative doses. Beeswax was used as phantom material. Rabbits were chosen at random without selection of race, color, sex or age. The skin of the smooth inner surface of the ear was irradiated.

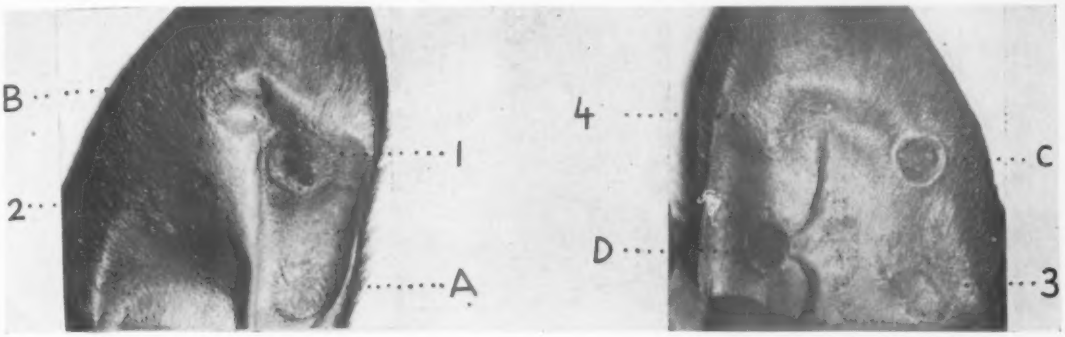
The experiments were planned as follows: Three to four control fields were irradiated with doses graded geometrically, the relation between highest and lowest dose being 2–4:1. The absolute value of the control doses was around 15,000 r. The test fields were irradiated through wax blocks of different thickness ranging from 0.3 to 15 mm. The doses applied were chosen so that the presumable depth dose would fall within the range covered by the control fields. The following may serve as an example (Table 1).

Control and test fields were arranged in a checkerboard pattern. For the irradiation, the ear was placed on a block of scattering medium. The tube, with or without wax block, was put firmly on the skin. All irradiations on one animal were given in one sitting of one to two hours' duration. There were five minute pauses between individual treatments.

During the weeks following the irradiation, the rabbits were examined at two to three day intervals by inspection and palpation. Photographs were taken but they usually failed to give as clear an impression

as the direct examination. Check-up examinations were repeated until the skin reactions reached optimum definition—usually about three weeks after irradiation. Occasionally, the observation period was extended until the lesions were healed.

At every examination, it was estimated—by comparison with the reaction on the control fields—which dose would have provoked, on the same rabbit, on direct irradiation, a reaction as seen on a test field. This dose we call the "equivalent dose." Its final determination was based on all estimates obtained during the period of observation. The percentage depth doses were calculated by expressing equivalent doses in terms of the doses delivered to the surface of the wax blocks (Fig. 2).



Rabbit No. 16, twenty-one days after irradiation.
Control Fields: *A*, 9000 r; *B*, 17,000 r; *C*, 22,700 r; *D*, 36,000 r.
Test Fields:

No.	Depth mm. of wax	Surface Dose	Equivalent Dose	Percentage Depth Dose
1	5.0	60,000 r	19,800 r	33
2	6.5	60,000 r	16,800 r	28
3	8.0	52,500 r	10,000 r	19
4	9.5	60,000 r	10,000 r	17

Fig. 2. Estimation of percentage depth dose.

RESULTS

The reaction of the rabbit's skin to roentgen rays is similar to that of the human skin. It begins with a diffuse erythema which reaches beyond the limits of the irradiated field. This disappears, and is followed by waves of erythema and pigmentation, sharply outlining the field.[3] With the doses used by us (about 15,000 r) the reactions go far beyond that degree. Edema and infiltration develop; often the fields show paradoxical paleness. The skin loses its gloss and becomes rough. Shrinking of the irradiated area occurs early, usually before ulceration. This is especially pronounced near the tip of the ear. Ulceration begins with one or two small ulcers or blisters, which, if doses of about 20,000 r and more have been applied, quickly extend over the whole field. The surrounding tissue forms an elevated wall around the sharply demarcated ulcer. After several weeks, the necrotic tissue sloughs off, leaving a smooth, epilated scar or a hole. The more rapidly the reaction develops, the quicker the healing sets in; thus it can frequently be observed that one field which received a high dosage is already healed while another to which less radiation was applied still

TABLE II

RESULTS OF DEPTH DOSE ESTIMATIONS

Rabbit No.	Date of Experiment	Date of Final Examination	Surface Dose (r)	Depth (mm. of beeswax)	Equivalent Dose (r)	Percentage Depth Dose
8	4-28-41	6-13-41	34,000	0.66*	19,000	56
8	4-28-41	6-13-41	24,000	0.66*	15,000	62
10	6- 1-41	6-16-41	48,000	7.5	14,400	30
11	6- 1-41	6-23-41	48,000	11.0	7,700	16
12	6-30-41	7-18-41	24,000	1.5	13,000	54
12	6-30-41	7-18-41	24,000	7.5	8,400	35
13	6-30-41	7-23-41	24,000	3.0	10,800	45
14	7-22-41	9-23-41	27,700	0.33	20,700	75
14	7-22-41	9-23-41	24,000	0.66*	15,100	63
14	7-22-41	9-23-41	19,100	0.66*	13,400	70
14	7-22-41	9-23-41	40,000	2.0	21,600	54
14	7-22-41	9-23-41	40,000	4.0	12,300	31
14	7-22-41	9-23-41	80,000	10.0	12.000	15
15	7-26-41	8-15-41	20,700	0.33	14,300	69
15	7-26-41	8-15-41	30,000	2.0	16,200	54
15	7-26-41	8-15-41	30,000	4.0	11,400	38
15	7-26-41	8-15-41	45,000	6.0	19,400	43
15	7-26-41	8-15-41	60,000	10.0	8,400	14
16	8-13-41	9-23-41	60,000	5.5	19,800	33
16	8-13-41	9-23-41	60,000	6.5	16,800	28
16	8-13-41	9-23-41	52,500	8.0	10,000	19
16	8-13-41	9-23-41	60,000	9.5	10,000	17
17-A	9-16-41	10-6-41	90,000	12.0	13,500	15
17-A	9-16-41	10-6-41	90,000	13.5	15,300	17
17-A	9-16-41	10-6-41	90,000	15.0	7,200	8
19	9- 5-41	9-23-41	80,000	7.0	22,400	28
19	9- 5-41	9-23-41	80 000	7.5	18,400	23
19	9- 5-41	9-23-41	80,000	8.0	16,800	21
19	9- 5-41	9-23-41	80,000	8.5	10,400	13

* No wax block was used in these cases; instead, reactions on exit fields were compared with those produced on direct irradiation The thickness of rabbits' ears (= depth of exit fields) is 0.5 to 0.75 mm. There might be a physiological difference between these and the other experiments.

shows a florid reaction. On albinos, the reactions are more difficult to follow as there is no pigmentation.

Equal doses do not always produce identical reactions. Both the severity of the reaction and the speed with which it develops show pronounced individual variability on different rabbits. Even the sensitivity of a given individual is not the same on all places; there seems to be an increase of susceptibility from the base to the tip, and from the lateral to the medial margin of the ear. Both the individual and the local variability of dose-response relations decrease with increasing severity of the reaction. As long as there is only erythema and pigmentation, discrepancies between the degree of reaction and doses delivered are not infrequent; with ulcerative reactions, the parallelism between dose and response is usually close.

No significant differences were observed in the speed with which test and control reactions developed during the period of observation. The estimates of equivalent doses as obtained on various days are not absolutely constant. The farther the reaction develops, the narrower become the

limits of variation. Reactions which are similar after ulceration has occurred will usually remain so throughout all further stages.

The results of the experiments used to estimate the depth dose distribution are given in Table II.

These results are graphically represented in Figure 3. The curve is drawn to fit best the experimental data.

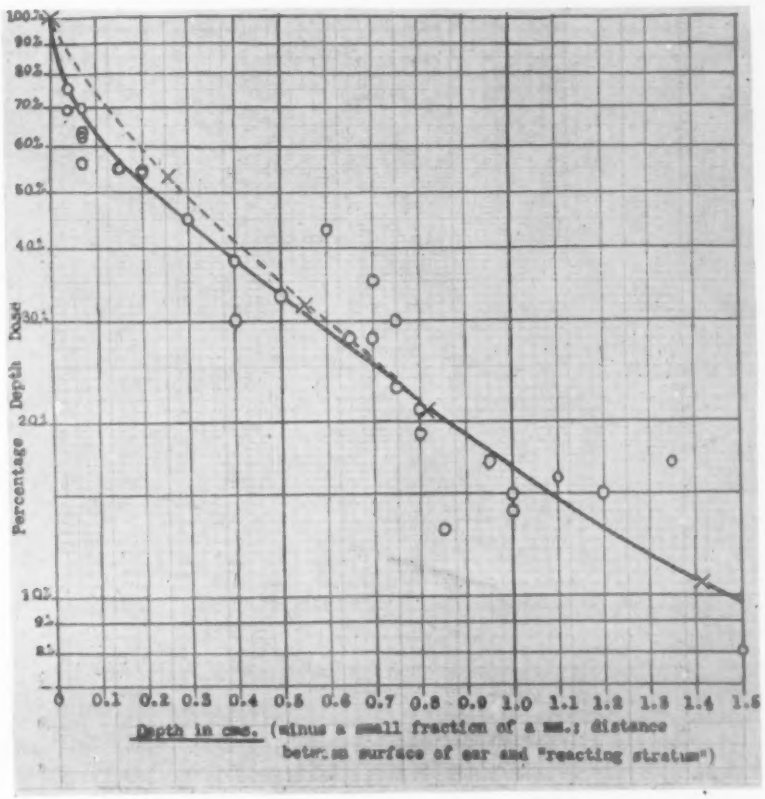

Percentage Depth Dose
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5
Depth in cms. (minus a small fraction of a mm.: distance
between surface of ear and "reacting stratum")

FIG. 3. Depth dose estimates. Contax apparatus, contact distance, no additional filter, localizer cone of 12 mm. in diameter. *Circles and full line:* rabbits' ear test. *Crosses and dashed line:* ionometric measurements with the extrapolation chamber (Quimby and Focht).

DISCUSSION

An attempt was made to keep the results as constant as possible by (1) determining the equivalent doses by comparing test and control fields on the same rabbit, thus eliminating the factor of individual variability; (2) arranging the fields in a checkerboard pattern, on the middle part of the ear, thus reducing the effect of local differences of susceptibility; (3) administering high doses, thus reducing variability as a whole. Yet the results obtained were not quite constant, which might be due to uncontrollable biological as well as physical factors. The probable error of a single experiment was estimated at 7 per cent (on the basis of 13 pairs of double determinations) or 13 per cent (from the deviations of single points from the curve). This is a tolerable error even for a single experiment. The curve as a whole, which is based on 29 experiments, is to be regarded as highly reliable.

Just what do these results mean? Strictly speaking, the curve is only a guide to pre-

dict the reaction of the skin on the rabbit's ear if irradiated through a layer of tissue, within the limits of our observations. The curve should not be considered a representation of the biological depth effects. On the basis of actual roentgen-biological knowledge we cannot expect any single depth dose curve to hold good for every biological reaction.[9] Neither is this curve analogous to the ionometric curves; a biological depth dose curve equals a physical one only under certain conditions.

Statements about physical depth doses made on the basis of biological studies are only inferential. The relation between r dose and response must be known to form an estimate of the reliability of the inference. In our experimental set-up, there are several factors likely to influence the dose-response relation: shape of field, pressure, time factor, field size, wave length factor. It is necessary to investigate these factors and analyze their respective effects.

Shape of Field. The isodose levels of the roentgen-ray beam produced by the contax apparatus are curved, the irradiated skin surfaces are flat. The dose, therefore, decreases markedly from the center to the periphery. The reaction is always strongest in the center. The degree reached there is used to evaluate the response. Hence, it is justifiable to regard the reactions observed in these experiments as responses to doses in the central beam.

Pressure. The cone, with or without wax block, was firmly set upon the rabbit's ear, causing considerable pressure. The possibility of this added mechanical trauma and disturbance of the circulation falsifying the surface dose-response relation had to be considered. In one rabbit (No. 9) pressure during irradiation was carefully avoided. Five irradiations were given, treating the inner surface twice and the outer surface three times. The reactions were observed on the five skin fields irradiated directly (input portal) and the five fields irradiated through the thickness of the ear (exit portal). The differences between the reactions on input and exit portals were the same whether pressure had been applied to the input portal (as usually) or not (as in rabbit No. 9). Thus, there was no evidence of pressure influencing the response to irradiation.

Time Factor. If the reaction of the human skin were used to determine depth dose distributions, time factors could become manifest in two ways: the curve could be steeper than the physical one,[11] and this deviation could be the more accentuated the more severe the test reaction. It has been demonstrated—within certain limits—that the smaller the intensity, the higher the dose necessary to produce a certain response on the human skin.[5] The depth effect—as determined by the human skin reaction—would therefore decrease not only by a diminution of the dose, but also by a reduction of the intensity as well. Thus, the depth "skin" dose curve would be steeper than the depth "r" dose curve. The influence of intensity seems to rise with increasing severity of reaction. Holthusen and Braun[5] state that the intensity factor becomes more pronounced as one proceeds from epilation dose over erythema dose to tolerance dose. If this is the case, the deviation of "skin" dose from r dose will be the greater, the higher the equivalent dose. We did a few experiments (rabbits No. 22–27) to see whether lengthening of the irradiation time within the limits of our observations would cause a marked change of the response; it was found that it did not. To investigate the time factor related to the severity of the reaction, it was determined whether depth doses found with high equivalent doses are significantly lower than those obtained with low ones. Here, too, the result was negative. Accordingly, there seems to be no appreciable influence of any time factor within the range of our observations.

Field Size Factor. The diameter of the field increases rapidly in the depth (at a depth of 7 mm. the surface of the area is about doubled). It is possible that the field size (independent from scatter) influences the

response. The results of preliminary experiments (rabbits No. 20–21) show that it does not cause any significant change within the limits of our experiments.

Wave Length Factor. The quality of the roentgen-ray beam emitted by the Contax apparatus presumably changes rapidly in the depth, especially in the layers near the surface. Whether or not this affects the r dose response relation in our case could not be investigated.

CONCLUSIONS

It has been demonstrated that the depth dose curve based on the reaction of the rabbit's ear is (1) reasonably exact and (2) presumably identical with or very similar to an ionometric depth dose curve (except for possible wave length factors). The curve can therefore be compared with those obtained by physical measurements. On doing so one sees that the "rabbit ear curve" is almost the same as the curve found by Quimby and Focht[10] on measurements with the extrapolation chamber (dotted line in Figure 3). Only for the first 5 millimeters does the rabbit ear curve lie somewhat below the extrapolation chamber curve. The difference never reaches 15 per cent and could be eliminated completely by adding a fraction of a millimeter to our depth values. Such a correction seems to be justified because the depth doses with the extrapolation chamber are for distances to the middle of the chamber (i.e. to a point behind a 0.25 mm. layer of air), while in our case the distances are to the level of the skin where the reaction is produced (a fraction of a millimeter beneath the surface). Besides, there is a certain margin of error in the measurement of the thickness of the absorber. For these reasons, we believe that the discrepancy between extrapolation chamber and rabbit ear curve is insignificant.

We assume that extrapolation chamber and rabbit's ear yield identical results because both are flat. The chamber used for depth dose measurements in contact roentgen therapy has a diameter of 0.5 mm., while the "reacting stratum" of the rabbit's ear apparently includes a very thin layer, a fraction of a millimeter beneath the surface. The chambers used by other authors are considerably deeper and therefore less apt to register a steep decrease of intensity within a small space.

The finding that one of the ionometric curves conforms to the results of bio-assay rounds out the scope of this investigation—which was to check, by means of a biological reaction, the discrepant statements based on different ionometric methods. Agreement between one ionometric method and the biological reaction used was found within the range of observation (contact distance, no additional filter, field of 12 mm. diameter, depths up to 1.5 cm.). There is every reason to believe that the same agreement would be found with other conditions.

SUMMARY

1. The statements concerning physical depth dose distribution in contact roentgen therapy are discrepant.

2. A biological method of depth dose measurements in contact roentgen therapy was worked out. The test object used was the skin of the rabbit's ear. The depth dose was estimated by comparing reactions of areas irradiated directly with those treated through layers of beeswax.

3. This method of bio-assay proved to be comparable to ionometric measurements.

4. The results of the rabbit ear tests are almost identical with those obtained with the extrapolation chamber.

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Vol. 50, No. 5

A NEW MEDIUM FOR GALLBLADDER VISUALIZATION

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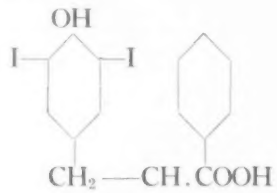
SINCE the introduction of the Graham test for visualization of the gallbladder and biliary passages by means of the sodium salt of tetraiodophenolphthalein, the diagnosis of gallstones and pathological conditions of the gallbladder has indeed made great advances. Though many synthetic products have been developed for the visualization of other body cavities, the tetraiodophenolphthalein salt has been utilized practically to the exclusion of others for gallbladder study. It has, however, been found to irritate the gastrointestinal tract, to have a disagreeable taste, often to cause nausea, vomiting, and diarrhea, and in a few cases collapse. In many instances the dye collects in the hepatic flexure obscuring the gallbladder. The increased employment of the double dose method, following its introduction by Stewart and Illick in 1934, has naturally intensified the search for a more satisfactory radiopaque substance.

We have recently had submitted for our approval a synthetic product with which as good visualization of the biliary passages is obtained as with the tetraiodophenolphthalein. This product is known commercially as priodax* and has proved most satisfactory in our experience. It is a white crystalline powder, odorless, insoluble in water, and soluble in ether-alcohol and acetone. The empirical formula is $C_{15}H_{13}O_3I_2$ containing 51.5 per cent iodine. It is chemically beta-(4-hydroxy-3,5-dioodophenyl)-alpha-phenyl-propionic acid, the structural formula of which is:



* Manufactured by the Schering Corporation, Bloomfield, New Jersey.

As may be seen from the structural formula, this preparation is not related to phenolphthalein.

Given in water, milk, grape or orange juice, it is swallowed while held in suspension, and when so taken it is tasteless. No one vehicle among those mentioned was found to offer any particular advantage. The tablets may also be swallowed whole. Chewing of the granules is undesirable as it produces a rather sharp, somewhat burning sensation in the throat. It is readily absorbed through the gastrointestinal tract, and carried apparently through the portal circulation to the liver, from whence it is excreted into the bile radicals, collecting in the gallbladder. Due to the rapid rate of intestinal absorption, we have encountered very little of the preparation in the colon fourteen hours after oral intake, so that at no time was it necessary to give an enema to clear the hepatic flexure in order to visualize the gallbladder, as so often happens with the tetraiodophenolphthalein salt.

The dosage has been 3 grams, given in six small tablets. According to Junkmann[2] from 61 to 83 per cent is excreted in the urine within seventy-two hours, whereas the sodium salt of tetraiodophenolphthalein is excreted mainly via the colon, usually causing considerable reaction. The iodine remains firmly in organic combination as it passes through the body so that no case of iodism was encountered. Up to the present time, owing to the high alkalinity of the solutions of the sodium salt of this product, it has not been found practical to employ the drug intravenously.

Under the name biliselectan, this substance has been experimented with by some of the European clinics for the past two years, with results apparently satisfactory (Grunke and Finger,[1] Lauer-Schmaltz,[3] and Rating[4]).

One hundred and thirty-four cases were critically analyzed; 94 female and 40 male. The vehicle employed for suspension of the preparation was water in 8 cases, fruit juice (orange or grape) in 35, and milk in 91 (Table I).

Visibility of the sac was good in 75 cases, fair in 19, poor in 12, and in 28 entirely absent. In 33 of the cases in which there was poor or non-visualization, a second dose was given the following night. Of these, 6 filled well, 5 fairly, 5 poorly, and 18 still presented no evidence of the medium. Of the latter, cholecystitis and/or stones were found at operation in 8 cases, 8 were discharged from the hospital with a diagnosis of chronic cholecystitis, and 2 remain well (Table II). It is worthy of note that the technique of prescribing a double dose, equaling 6 to 8 grams of the sodium salt of tetraiodophenolphthalein, was discarded, and but one 3 gram dose of priodax was given in all but the 33 cases above mentioned.

Table I

Sex	Female	Male
	94	40
Vehicle	Milk	Water	Fruit Juice orange or grape
	91	8	35

Table II

Gallbladder visibility	Good	Fair	Poor	None
Single dose	75	19	12	28
Double dose*	6	5	5	18

* Given for poor or non-visualization.

Table III

Contrast medium in bowel	None	Trace	Not Stated
	61	37	36

Sixty-one cases failed to reveal any of the opaque substance in the colon, 37 presented a questionable or faint trace, and in 36 instances the notation was omitted in our records. This omission occurred before it was observed that the bowel in most instances was unusually clear as compared with the studies made with the sodium salt of tetraiodophenolphthalein (Table III).

The reactions on the whole were extremely mild. In 43 cases there was none. Two patients complained of severe nausea, and 23 suffered nausea to a mild degree only. In most instances the information was obtained by questioning rather than volunteered (Table IV). There was moderate griping in 18 cases, and in 18 instances diarrhea, all mild in character with the exception of one. No instance of vomiting was encountered. Twenty-seven patients referred to a slight burning pain on urination the morning following the intake of the radiopaque substance. Following the initial bladder evacuation, no further discomfort was experienced. A burning sensation in the throat as the drug was swallowed was complained of in 32 cases. An effort was made to overcome this discomfort by administering the drug in sugar coated tablet form, but we did not find the complaint sufficiently annoying to prefer the discomfort to the patient of swallowing the tablets whole rather than prescribing it in suspension. There were 9 cases of epigastric disfort, and 5 patients suffered from headaches and dizziness.

Table IV

Reactions	None	Nausea		Vomiting	Diarrhea		Cramps	Burning at end of micturation*
		mild	severe		mild	severe		
	43	23	2	0	17	1	18	27

Burning in throat	Epigastric discomfort	Headaches and dizziness
32	9	5

* At the initial passing of urine the following morning only.

SUMMARY

A new synthetic compound, containing 51.5 per cent iodine in organic combination, commercially known as priodax, has been submitted to clinical tests in 134 cases. It is readily absorbed by the intestinal tract so that it rarely produces a shadow therein. It is simple of administration, readily acceptable to the patient, and has proved in our experience to be more desirable for the visualization of the gallbladder than the sodium salt of tetraiodophenolphthalein. Reactions have been negligible.

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SOME OBSERVATIONS ON PRIODAX*

A NEW CONTRAST MEDIUM FOR THE VISUALIZATION OF THE GALLBLADDER

By WILLIAM A. MARSHALL, M.D.
CHICAGO, ILLINOIS

GREAT progress has been made in recent years in the roentgenological examination of the gallbladder. The technique using tetraiodophenolphthalein has been improved considerably and in most cases good diagnostic roentgenograms can be obtained with this drug. However, it has certain disadvantages. One of them is the fact that the phenolphthalein acts as a cathartic and often produces premature elimination of the dye. Then a satisfactory filling of the gallbladder cannot be obtained and we do not know whether the failure of filling is due to a pathologic condition in the gallbladder or to the premature elimination of the dye. This disadvantage can be obviated through the intravenous use of the dye. However, the intravenous administration sometimes causes a rather severe reaction which makes this method impractical for ambulatory use. Another disadvantage is the fact that the absorption of the dye in the bowel is not perfect; only part of the dye is absorbed and if there is a pathological condition within the small intestine that impairs the absorptive function of the mucous membrane then the usefulness of the tetraiodophenolphthalein is still more impaired. Therefore, the attempt to produce a new and better contrast medium for the visualization of the gallbladder has never stopped. The following are the requirements of a good gallbladder contrast medium:

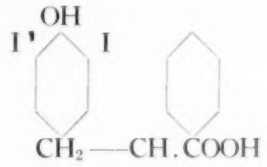
1. It must not be toxic and particularly the iodine part of it must be sufficiently closely bound to the organic constituent of the molecule so as to prevent liberation of the iodine thus causing iodism.

2. The contrast medium must be to an appreciable extent excreted through the liver.

3. The molecule of the contrast medium must be large enough so that in the process of re-absorption in the gallbladder only the water is re-absorbed and not the medium. Ordinarily no contrast medium is heavy enough to produce a satisfactory gallbladder image in normal bile concentration. Only through the constant re-absorption of water from the gallbladder, and therefore through the constantly increased concentration of the medium in the gallbladder, does the shadow become roentgenologically distinct.

4. The contrast medium should be readily absorbable in the small intestine and it should not act as a laxative so that the intestine will have time enough to absorb most of the medium.

Using these postulates as a basis Dohrn and Diedrich have produced a number of iodine-containing substances which were tested for their qualities as gallbladder contrast media. All in all, at least 28 various substances were produced. Outstanding among them was priodax, a beta-(4-hydroxy-3, 5-diiodophenyl)-alpha-phenyl-propionic acid. The formula is



or $C_{15}H_{13}O_3I_2$.

Priodax is a white powder soluble in alcohol and ether and practically insoluble in water. The sodium salt is well soluble in

* Priodax is made by the Schering Corporation, Bloomfield, New Jersey, and is now commercially available.

water. Priodax contains 51.5 per cent iodine.

Junkmann[2] has made extensive experiments on rabbits with priodax and he has come to the following conclusions: The average lethal dose for priodax is 0.39 gm. per kilogram of animal body weight if used intravenously and 1.1 gm. per kilogram if used by mouth. The lethal dose of tetraiodophenolphthalein per kilogram of animal body weight is 0.31 gm. if used intravenously and 2.8 gm. per kilogram if used by mouth. These findings seem to show that of the two contrast media tetraiodophenolphthalein is more toxic if given intravenously and priodax is more toxic if given by mouth. This is, however, only apparent. Tetraiodophenolphthalein is not nearly so well absorbed in the bowel as priodax and therefore a much larger amount of tetraiodophenolphthalein has to be given to produce a toxic result. The intravenous administration proves that of the two the priodax is less toxic. Other differences between the two media are in their final disposal by the human system. It has been shown that most of the priodax is eventually excreted through the urine and seventy-two hours after ingestion in man 61 to 83 per cent of it was recovered in the urine. Of tetraiodophenolphthalein only small traces have been recovered in the urine, which makes it probable that most of the tetraiodophenolphthalein is excreted through the intestines. Tetraiodophenolphthalein has a severe purgative action and therefore much of the dye is excreted before it is absorbed. Priodax has very little or no purgative action and therefore the absorption is much more complete. But even if the purgative action of

Fig. 1. Gallbladder visualization with tetraiodophenolphthalein. The gallbladder shadow is not very dense due to poor absorption of the contrast medium in the intestines and it is not clear due to the superimposition of the unabsorbed medium upon the gallbladder.

Fig. 2. Gallbladder visualization with priodax on the same patient a few days later, all other factors being exactly the same. The gallbladder shadow is quite dense due to almost complete absorption of the contrast medium and clear due to the absence of disturbing superimposed colon shadows.

tetraiodophenolphthalein is neutralized by the simultaneous administration of paregoric, priodax will be better absorbed than tetraiodophenolphthalein.

The following observations are based on the first 50 gallbladder examinations in which priodax was used. The double dose method was employed exclusively. The patient was instructed to take six priodax tablets immediately after a light luncheon at about 1 P.M. Then nothing but water was given by mouth until 8 P.M. At 8 P.M. the patient was instructed to eat a fat-free meal consisting of dry toast and tea without cream and sugar and then the other six priodax tablets were taken. Nothing was given by mouth except water until 9 A.M. the following day. The first roentgenograms were taken then. Following this examination a fat-protein meal was given and a check-up roentgenogram was taken two hours later. The patient was instructed to swallow the tablets whole and not to chew them because it has been reported that if the tablets are chewed some acid is liberated which has a disagreeable taste.

Our experiences with priodax have been very satisfactory. Of the 50 patients only one vomited and she was a neurasthenic who might have vomited for some other reason. Most patients had several bowel movements but only one complained of rather severe diarrhea. Two patients mentioned that they observed some burning on urinating. No other side effects were observed.

The visualization of the gallbladder was considerably better than with the other contrast media because the absorption of priodax within the intestines was practically complete and therefore there were no disturbing colon shadows superimposed upon the gallbladder.

Of the 50 patients, 15 were found to have a normal gallbladder. In the other 35 cases some abnormality was observed. Insufficient contraction, i.e., poor function was noted in 8; faint visualization was noted in 1 patient only; enlargement of the gallbladder but satisfactory function in 6; distortion of the gallbladder due to adhesions, 1 case; no visualization was obtained in 4 cases; positive stone shadows and no visualization of the gallbladder in 6 cases; stones and visualization of the gallbladder in 6 cases.

Of the 4 cases in which the gallbladder was not visualized 2 were operated on and a pathological gallbladder was found in both.

Of the 12 cases in which gallstones were diagnosed, 7 were operated on and the roentgen diagnosis was fully confirmed in every case.

CONCLUSION

Priodax is a valuable contrast medium for the roentgenological visualization of the gallbladder. It has the following advantages over tetraiodophenolphthalein: (1) it is less toxic; (2) it produces fewer disagreeable side effects; (3) it does not act as a purgative; (4) it is almost completely absorbed in the intestines thus obviating disturbing colon shadows superimposed upon the gallbladder.

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Vol. 50, No. 5

THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

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Publisher: Charles C Thomas, 220 East Monroe Street, Springfield, Illinois.

Issued Monthly. Subscription $10.00 per year, $11.00 in Canada and $12.00 in foreign countries. Advertising rates submitted on application: Editorial office, 110 Professional Building, Detroit, Mich., Office of publication, 220 E. Monroe Street, Springfield, Ill. Information of interest to all readers will be found on page iv.

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Twenty-eighth Annual Meeting: 1943, cancelled.

EDITORIALS

WAR WOUNDS AND INJURIES OF THE CHEST

EDWARDS, in a critical review of war wounds and injuries of the chest,[1] calls attention to the relatively low incidence of chest wounds admitted to ambulances and casualty clearing hospitals during the first World War. He states that there has apparently been an increase in the relative incidence in the more recent campaigns and calls attention to the problem of the diagnosis and treatment of chest wounds and injuries in the present war which is so widely spread over the face of the earth. Not only are the soldiers participating in campaigns victims of the high explosives and shells but the indiscriminate bombing of cities and towns has increased enormously the injuries to the chest. Not only are these injuries confined to the healthy and more vigorous portions of the population but both sexes and all ages are victims.

For descriptive purposes Edwards divides his chest injuries into two groups, namely the non-penetrating and penetrating type of injury.

In the non-penetrating injuries of the chest the incidence is far greater in the present war than in the last, and this increase is brought about by the widespread bombing as well as being partially due to the enormous mechanization of all services increasing the numbers of accidental injuries. These non-penetrating injuries of the chest vary from the minor contusions of the chest wall to the complete crushing of the chest. In the younger subjects the resilience of the bones and cartilages of the thorax permit considerable deformity before fracture takes place and there may be a widespread intrathoracic damage without demonstrable injury to the chest wall.

The simple fractures such as one encounters in civilian life are of course met with frequently in the armed forces. The fractures may be of a simple type without injury to the pleura or to the lung.

Edwards points out the importance of a thorough examination of the chest as well as the spine in injuries to the chest wall as not infrequently there are associated fractures especially of the scapula and clavicle, and compression fractures of the dorsal spine may occur without being evident as the pain occasioned by the rib fracture may mask the more serious spinal injury.

In addition to the damage which may occur to the veins and chest wall, contusions and lacerations of the lungs are relatively common and hematomas may occur, giving well defined multiple smaller diffuse shadows in the lungs on roentgenological examination. Not only may there be demonstrated the hematoma involving the lung itself but frequently a quantity of blood may be found in the intrapleural spaces. Lobar or massive collapse of the lung may occur on the side of the injury or in the contralateral lung due to blood or thick mucus in the bronchi and to the inability of the patient to cough.

Surgical emphysema over a localized area is relatively common in non-penetrating injuries and it may at times be more widespread, passing up in the muscle planes and subcutaneous tissues to the neck and face. The escape of air into the pleura may lead to a "tension pneumothorax" with acute symptoms of mediastinal displacement.

One of the rare complications of chest injuries is mediastinal emphysema. This results from damage to larger bronchi or to the trachea, the air passing up in the mediastinal tissue to escape through the up-

[1] Edwards, A. T. War wounds and injuries of the chest. *Brit. J. Surg.*, July, 1943, 31, 74-86.

per aperture of the thorax into the deep and superficial tissues of the neck.

Reference is made in the report regarding deaths of soldiers on the battle field in the 1914–1918 war in which blood-stained fluid was found in the mouth and nose and there was no obvious gross injury to the chest wall. The pathology of this type of death was not generally recognized, but with the increasing number of cases at the present time as a result of widespread and indiscriminate bombing further light has been shed on the causation and pathology of this type of injury.

Zuckermann and others have carried on extensive animal experimentation in association with blast injuries and it has been shown that there may be widespread pulmonary lesions complicated by atelectasis or collapse and consolidation as shown in the roentgenological examination.

The disproportion between the frequency of chest symptoms and physical signs in contrast to the roentgenological demonstration of intrathoracic lesions has been frequently stressed.

Williams has clearly demonstrated the differences between the effects of blasts in water and air and points out that injury may be sustained over much greater distances in water. In blast injuries in water the usual area of the abdominal cavity involved, if visceral perforation occurs, is the lower half and all the physical signs point to the lower abdomen in such a type of injury, whereas rigidity and tenderness of the upper abdomen usually indicate blast injury of the lung and not an intra-abdominal lesion. It is pointed out by all observers that the roentgenological signs which show as multiple shadows or mottling throughout one or both lungs appear early and are due to alveolar and interstitial hemorrhages.

As might be expected, the penetrating wounds of the pleural cavity produce multiplicity of variations, depending upon whether the injury is caused by a bullet or a fragment. Bullet wounds often give rise to little or no disturbance other than the initial injury, whereas the large shell or bomb fragments which occasion numerous lacerations may lead to widespread damage and death. It is pointed out that the prognosis is better in anteroposterior than in transverse wounds and in wounds of the middle zone of the hemithorax than in those at the apex or base.

One of the more serious complications of injuries to the chest is the occurrence of a hemothorax, which may follow non-penetrating wounds, closed penetrating wounds and closure of open pneumothorax or after thoracotomy for gunshot wounds. It is one of the most frequent complications of wounds and injuries of the chest. It is pointed out that the proportion of patients with penetrating wounds of the chest who develop hemothorax is much higher in war casualties than in the civilian population. The diagnosis of hemothorax in closed injuries of the chest may be quite readily made from the roentgenographic studies by the signs of pleural effusion and the ground-glass appearance of the affected side.

The widespread changes from the minimal to the most exaggerated type of pathology that may occur in the lungs following blast injuries or penetrating wounds of the chest point to the importance of the use of roentgen rays in the diagnosis of chest injuries. Edwards states that too much emphasis cannot be placed on the necessity for the use of roentgen rays in diagnosis in chest injuries in war, pointing out that physical signs may be most deceptive and accurate diagnosis becomes more and more dependent upon the roentgen ray for the exact information which is essential in the control of chest wounds from the time of the injury until the patient is convalescent. Too frequently in the past many medical men have stressed the difficulties rather than the advantages of the roentgen ray, but with the modern portable apparatus much less discomfort is caused the patient by roentgen examination than by attempts at complete clinical examinations of the chest. The importance is stressed of vary-

ing the type of examination and the fact that more useful information is given if the patient is roentgenographed in the sitting than in the lying posture and, as might be expected, the necessity of lateral examinations of the chest is emphasized.

Since so much depends upon the roentgenological studies of chest injuries there is an imperative necessity of a knowledge of the roentgen appearance of the various types of chest injuries incurred not only in the zone of battle but also in the civilian population.

AXEL P. BERGMAN

1869-1943

DR. AXEL P. BERGMAN, of New Haven, Connecticut, a member of the American Roentgen Ray Society since 1909 died on June 18, 1943.

Dr. Bergman was born in Stockholm Sweden, May 2, 1869. He received the degree of Bachelor of Science from the Stockholm Real Gymnasium in 1888. He served in the Swedish Army for two years, in the heavy artillery. In 1890 he came to the United States and in 1895 he received the degree of Doctor of Medicine from New York University, after which he spent a year as intern in Bellevue Hospital. From 1896 to 1899 he practiced in Cooperstown, New York, and he engaged in general prac-

tice in New Haven, Connecticut, for the following ten years. After a year in Philadelphia with the late Dr. Charles L. Leonard, Dr. Bergman returned to New Haven as the first roentgenologist in that city. Until 1918 he was on the staff of the New Haven Hospital, and until his death he was roentgenologist to the Hospital of St. Raphael. His society affiliations, in addition to the American Roentgen Ray Society, included the New Haven Medical Society, of which he was a past president, the Connecticut Medical Society, the American Medical Association, and the Radiological Society of North America. He was a 32d degree Mason.

Dr. Bergman is survived by his daughter, Mrs. Gertrude B. Stanio, who was his technician for twenty-five years. The staff of the hospital where he served and died paid tribute to him in a resolution stating: "Dr. Bergman was a credit to his profession and he showed those qualities in his daily work that deeply and favorably impressed those with whom he was associated. He made his place among the most successful roentgenologists in this State. His ethical, honest, unprejudiced and exacting behavior, as well as his broad understanding of all problems never failed him even in his last illness, when he showed great patience and an upright sterling character, never complaining, but bearing his lot with an unusual degree of fortitude. He lived his life well."

Ramsay Spillman

GEORGE C. CHENE
1882-1943

IN THE death of Dr. George C. Chene, Detroit has lost one of its earliest and most able radiologists. He died on August 31, 1943, after a long and disabling illness.

Dr. Chene was a direct descendant of Pierre Chene, one of the adventurous group of explorers in the party of Sieur de la Mothe Cadillac who founded Detroit in 1701, and for whom Chene Street was named. He was born in Windsor, Ontario, in 1882. He was educated at the Windsor Collegiate Institute and received his medical degree from the Detroit College of Medicine in 1905. After his internship at St. Mary's Hospital, Detroit, he became associated with the late Dr. Preston M.

Hickey, specializing in roentgenology, and thereafter he limited his practice to radiology. He established the first x-ray laboratories at St. Mary's and Providence Hospitals, Detroit, and at the Hotel Dieu in Windsor, Ontario. Upon his retirement from active duty at Providence Hospital, he was honored by the staff with a public banquet at which he was the recipient of the honor plaque for long and faithful service. For many years he was a faculty member of the Detroit College of Medicine and Surgery and a staff member of St. Mary's, Receiving, Eloise, and Providence Hospitals, either as attending or consulting radiologist. He was a member of the Detroit Roentgen Ray and Radium Society, the Radiological Society of North America, the Wayne County Medical Society, the Michigan State Medical Society and the American Medical Association. A highly prized social and scientific connection was his long-standing membership in the Prismatic Club.

For a number of years Dr. Chene had been increasingly disabled from the effects of long exposure to roentgen rays and radium, but with the courage and fortitude of the true physician he had borne unremitting pain, several amputations, and the knowledge of early final disaster without flinching and without complaint.

Dr. Chene was impartially scientific in his work. He aimed to make no hurried or snapshot diagnoses. His material was most thoughtfully considered before his final interpretation, and only those who were closely associated with him know the care and study he spent on his films. His decisions were rendered with conviction born of long and wide experience.

His relations with his professional friends were always exceptionally cordial and no one could be more solicitous of their welfare. Dr. Chene was ever the genial companion and with his ready wit he was a natural center of any group. His code permitted neither sham nor bluff and he found special delight in exposing the one and puncturing the other. He never reneged in the game of life, which he played fairly and squarely in accordance with the highest rules of honor.

All his life Dr. Chene was attracted by the theater and he rarely missed being a first-nighter. As a genius might repeat long passages of once-heard music, Dr. Chene could repeat a play in miniature with astounding artistry and perfection to the delight of his companions. He displayed a rare personality without pomp, a dignity without show or pretense, charity and good will to his fellow men without patronizing airs, and faith without formality in all that is good. We who knew him well rejoiced in his good company and mourn the passing of a respected, generous and honorable colleague.

R.A.C. Wollenberg

HAIG HAIGOUNI KASABACH
1898-1943

DR. HAIG H. KASABACH died on September 1, 1943, in the Neurological Institute, New York.

Dr. Kasabach's colleagues knew that he had been through hardships in the old country ranking with the Forty Days of Musa Dagh, but he seldom made any reference to them, and he seemed to prefer to put them behind him. He seems not even to have written them down for his children. From his nephew, Dr. Vahram Kasabach of Detroit, it is learned that Haig was born in Sivas, Turkey, the seventh of eight children of an important government official in the Armenian community. During the first World War the whole family

was deported, and in the course of the Turks' activities, Haig was beaten and left for dead. After recovering consciousness, he made his way back to Sivas, living on grass and wild fruits on the way. On his return he found sanctuary with friends and former teachers of the American missionary school, who nursed him through a pneumonia induced by the rigors of his travels by night. When the Turks learned of his return, he secretly made his way to Amasia to the home of the widow of his eldest brother, a victim of the Turks.

At the end of the war, he became a music teacher in a government school, and aided his sister-in-law in organizing an Armenian school, for which he labored unceasingly. Feeling that further education would increase his capacity for usefulness, he came in 1920 to the United States. After working a short time in New York he went to Ann Arbor and earned his way through the University of Michigan, graduating with high honors from the Medical School in 1926. He served his internship in the University Hospital and became a member of that able group trained in radiology by Hickey. He came to the Presbyterian Hospital in New York on April 1, 1929, and was immediately accepted by the entire New York group of radiologists as a welcome acquisition and a productive investigator. He was Assistant Professor of Radiology at Columbia University. He served the New York Roentgen Society as treasurer in 1942–1943 and in the spring of 1943 was elected secretary. Dr. Kasabach was a member of the American Roentgen Ray Society, the New York County and State Medical Societies, and the American Medical Association. He was a Fellow of the American College of Radiology.

Dr. Kasabach was married in 1934 to Miss Erna Koeber of Pennsville, Pennsylvania, who survives him, with a daughter, Arlynn, aged seven, and a son, Haig Fred, aged five.

For about a year before his death, he had a severe hypertension, which masked the symptoms of an acoustic neuroma. In his short life of not quite forty-five years, he achieved a great deal and won an enduring place in the hearts of all who knew him.

Ramsay Spillman

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer.

MEETINGS OF ROENTGEN SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. H. Dabney Kerr, University Hospital, Iowa City, Iowa. Annual Meeting: 1943, cancelled.

American College of Radiology
Secretary, Mac F. Cahal, 540 N. Michigan Ave., Chicago, Ill.

Section on Radiology, American Medical Association
Secretary, Dr. J. T. Murphy, 421 Michigan St., Toledo, Ohio. Annual meeting: 1943, cancelled.

Arkansas Radiological Society
Secretary, Dr. J. S. Wilson, Mack Wilson Hospital, Monticello, Ark. Meets every three months and also at time and place of State Medical Association.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting: Drake Hotel, Chicago, Ill., Executive Sessions only, Dec. 1–2, 1943.

Radiological Section, Baltimore Medical Society
Secretary, Dr. Walter L. Kilby, Baltimore. Meets third Tuesday each month, September to May.

Section on Radiology, California Medical Association
Secretary, Dr. J. D. Coate, 434 Thirtieth St., Oakland, Calif.

Radiological Section, Connecticut Medical Society
Secretary, Dr. Max Climan, 242 Trumbull St., Hartford, Conn. Meets bi-monthly on second Thursday, at place selected by Secretary. Annual meeting in May.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. H. W. Ackemann, 321 W. State St., Rockford, Ill.

Radiological Section, Los Angeles County Medical Association
Secretary, Dr. Donald R. Laing, 65 North Madison Ave., Pasadena, Calif. Meets on second Wednesday of each month at the County Society Building.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Brooklyn Roentgen Ray Society
Secretary, Dr. Leo Harrington, 880 Ocean Ave., Brooklyn, N.Y. Meets monthly on fourth Tuesday, October to April.

Buffalo Radiological Society
Secretary, Dr. Joseph S. Gian-Francheschi, 610 Niagara St., Buffalo, N. Y. Meets second Monday of each month except during summer months.

Chicago Roentgen Society
Secretary, Dr. Warren W. Furey, 6844 S. Oglesby Ave., Chicago, Ill. Meets second Thursday of each month October to April inclusive at the Palmer House.

Cincinnati Radiological Society
Secretary, Dr. Samuel Brown, 707 Race St., Cincinnati, Ohio. Meets third Tuesday of each month, October to May, inclusive.

Cleveland Radiological Society
Secretary, Dr. J. O. Newton, 13921 Terrace Rd., East Cleveland. Meets at 6:30 P.M. at Midday Club on fourth Monday each month, October to April, inclusive.

Denver Radiological Club
Secretary, Dr. Edward J. Meister, 366 Metropolitan Bldg., Denver, Colo. Meets third Friday of each month at Denver Athletic Club.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Building.

Florida Radiological Society
Acting Secretary, Dr. Walter A. Weed, 204 Exchange Bldg., Orlando, Fla. Meetings in May and November.

Georgia Radiological Society
Secretary, Dr. James J. Clark, 478 Peachtree St., Atlanta, Ga. Meets in November and at annual meeting of Medical Association of Georgia in the spring.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month at a place designated by the president.

Illinois Radiological Society
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. H. C. Ochsner, Methodist Hospital, Indianapolis. Meeting held the second Sunday in May annually.

Kentucky Radiological Society
Secretary, Dr. W. C. Martin, 321 W. Broadway, Louisville. Meets annually in Louisville on first Saturday in Apr.

Long Island Radiological Society
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:30 P.M.

Louisiana Radiological Society
Secretary, Dr. J. R. Anderson, 1130 Louisiana Ave., Shreveport. Meets annually during Louisiana State Medical Society Meeting.

Michigan Association of Roentgenologists
Secretary, Dr. E. M. Shebesta, 1429 David Whitney Bldg., Detroit. Three meetings a year, Fall, Winter, Spring.

Milwaukee Roentgen Ray Society
Secretary, Dr. C. A. H. Fortier, 231 W. Wisconsin Ave., Milwaukee, Wis. Meets monthly on second Monday at University Club.

Minnesota Radiological Society
Secretary, Dr. Annette T. Stenstrom, 1218 Medical Arts Bldg., Minneapolis, Minn. One meeting a year at time of Minnesota State Medical Association.

Nebraska Radiological Society
Secretary, Dr. D. A. Dowell, Medical Arts Bldg., Omaha, Nebr. Meets third Wednesday of each month, at 6 P.M. at either Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Hugh F. Hare, Lahey Clinic, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

Radiological Society of New Jersey
Secretary, Dr. H. J. Perlberg, 921 Bergen Ave., Jersey City. Meets annually at time and place of State Medical Society. Mid-year meetings at place chosen by president.

New York Roentgen Society
Secretary, Dr. Ramsay Spillman, 115 East 61st St., New York City. Meets monthly on third Monday, New York Academy of Medicine, at 8:00 P.M.

North Carolina Roentgen Ray Society
Secretary, Dr. Major Fleming, Rocky Mount, N. C. Annual meeting at time and place of State Medical Society. Mid-year scientific meeting at place designated.

North Dakota Radiological Society
Secretary, Dr. L. A. Nash, St. John's Hospital, Fargo. Meetings held by announcement.

Central New York Roentgen Ray Society
Secretary, Dr. C. F. Potter, 820 S. Crouse Ave., Syracuse. Three meetings a year. January, May, November.

* Secretaries of Societies not here listed are requested to send the necessary information to the Editor.

Ohio Radiological Society
Secretary, Dr. J. E. McCarthy, 707 Race St., Cincinnati. Meets at time and place of annual meeting of Ohio State Medical Association.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. L. E. Wurster, 416 Pine St., Williamsport.

Philadelphia Roentgen Ray Society
Secretary, Dr. R. P. Barden, University Hospital, Meetings first Thursday of each month from October to May inclusive at 8:15 P.M., in Thompson Hall, College of Physicians, 19 S. 22d St.

Pittsburgh Roentgen Society
Secretary, Dr. R. G. Alley, 4800 Friendship Ave. Meets second Wednesday each month, 4:30 P.M., October to June, Pittsburgh Academy of Medicine.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Sidney Larson, Strong Memorial Hospital. Meets monthly on third Monday from October to May, inclusive, 8 P.M. at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. A. M. Popma, 220 N. First St., Boise, Idaho.

St. Louis Society of Radiologists
Secretary, Dr. P. C. Schnoebelen, 462 N. Taylor Ave. Meets fourth Wednesday of each month, except June, July, August, and September, at a place designated by the president.

San Francisco Radiological Society
Secretary, Dr. H. A. Hill, 450 Sutter St., San Francisco. Meets monthly on third Thursday at 7:45 P.M., first six months at Toland Hall, second at Lane Hall.

Shreveport Radiological Club
Secretary, Dr. R. W. Cooper, Charity Hospital, Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

South Carolina X-Ray Society
Secretary, Dr. T. A. Pitts, Baptist Hospital, Columbia, S. C. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

Tennessee Radiological Society
Secretary, Dr. J. M. Frère, 707 Walnut St., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. Herman Klapproth, Sherman, Texas.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets every Thursday from 4:00–5:00 P.M., Room 301, Service Memorial Institute.

Virginia Radiological Society
Secretary, Dr. E. L. Flanagan, 116 E. Franklin St., Richmond, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Thomas Carlile, 1115 Terry St., Seattle. Meets fourth Monday each month, October throughMay, College Club, Seattle.

X-ray Study Club of San Francisco
Secretary, Dr. J. M. Robinson, University of California Hospital. Meets monthly in evening on third Thursday.

Cuba

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Meets monthly on third Thursday from November to June inclusive, at 8:15 P.M., 32 Welbeck St., London.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets on the third Friday of each month during the winter at 8:15 P.M. at the Royal Society of Medicine 1, Wimpole St., London, W. 1.

Faculty of Radiologists
Secretary, Dr. M. H. Jupe, 32 Welbeck St., London, W. 1 England.

Section of Radiology and Medical Electricity, Australasian Medical Congress
Secretary, Dr. H. M. Cutler, 139 Macquarie St., Sydney, New South Wales.

Radiological Section of the Victorian Branch of the British Medical Association
Secretary, Dr. Keith Hallam, St. George's Hospital, K.E.W., Melbourne, E. 4, Victoria, Australia. Meets monthly from March to November inclusive.

Canadian Association of Radiologists
Secretary, Dr. A. D. Irvine, 540 Tegler Bldg., Edmonton, Alberta.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Radiological Section, New Zealand British Medical Association
Secretary, Dr. Colin Anderson, Invercargill, New Zealand. Meets annually.

South America

Sociedad Argentina de Radiologia
Secretary, Dr. Guido Gotta, Buenos Aires, Argentina. Meetings are held monthly.

Continental Europe

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

Société Suisse de Radiologie (Schweizerische Röntgen-Gesellschaft)
Secretary for French language, Dr. A. Grosjean La Chaux de Fonds.
Secretary for German language, Dr. Scheurer, Molzgasse Biel. Meets annually in different cities.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banul Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad: USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock, State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly, first Monday, 8 P.M.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Vol. 50, No. 5

DEPARTMENT OF TECHNIQUE

Department Editor: Robert B. Taft, M.D., B.S., M.A., 103 Rutledge Ave.
Charleston, S. C.

LATERAL ROENTGENOGRAPHY OF THE SPINE

By CESARE GIANTURCO, M.D.
Carle Hospital Clinic
URBANA, ILLINOIS

THE failure to understand the anatomical principles involved in the taking of lateral roentgenograms of the spine has caused the spoilage of many films. Most technicians strive to place the spine parallel with the table. Figure 1 shows that in this position only few vertebrae will be shown in true profile while the others will be distorted and overlapping.

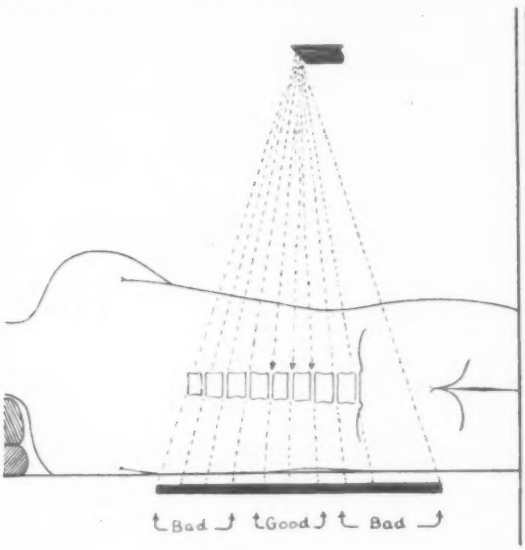

Fig. 1

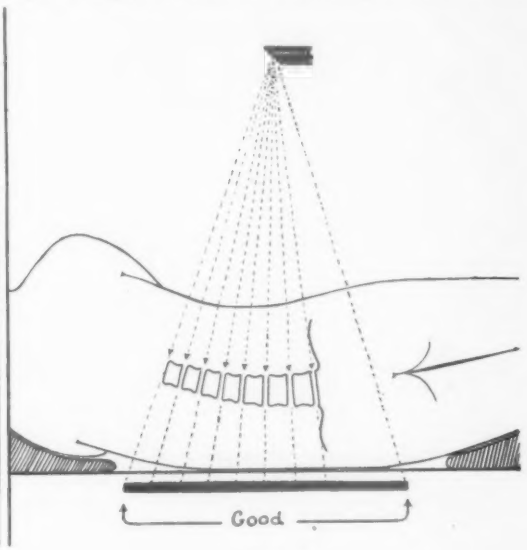

Fig. 2

The only way of obtaining consistently good lateral roentgenograms of long segments of the spine is as follows: *All the vertebrae to be shown must be at the same distance from the focal spot.* Figure 2 shows that this position will allow the rays to enter all the intervertebral spaces and all the vertebrae will be shown in true profile.

In practice, this is accomplished by holding one end of a string or of a yardstick against the side of the roentgen tube at the level of the focal spot and moving the tube toward the head or toward the feet of the patient until the spinous processes of the uppermost and lowermost vertebrae to be shown in the film are equidistant from the focal spot. Once this is accomplished, the spine is given such a curvature that the intervening spinous processes will also be equidistant from the focal spot. This is done by elevating the legs or the shoulders, or both, with sandbags and pillows.

If it is impossible to give the spine the proper curvature, then it is also impossible to obtain good lateral roentgenograms of long vertebral segments and one should be content with small films showing only two or three vertebrae at a time. In this case, the central ray should be perpendicular to a line joining the spinous processes of the few vertebrae to be shown.

PYROGRAPHIC MARKING OF ROENTGEN FILMS

By LIEUTENANT COLONEL PETER J. KAPO, M.C., A.U.S.

AN ACCESSORY, simple method for permanently marking films is made feasible by pyrography. A wood-burning set, costing less than one dollar, serves the purpose admirably. A radiator-like tip found in the author's set functioned indefinitely without overheating. An illustration (Fig. 1) of the stylus with handle and electric cord is shown. Within a few minutes after plugging in, the tip becomes sufficiently heated to commence inscribing roentgen films. The result is a pyrographic impression simulating the appearance of white ink writing. If desired, the inscription may be printed in any one of variety of colors by interposing the respective type of foil such as gold, silver, green, blue and red, as illustrated (Fig. 2). The top three lines of the inscription show the result obtained without using foil.

The technique requires the customary serial numbering of roentgenograms with lead markers and only after the film is completely processed and dried are the pyrographic entries made. Direct or oblique lighting facilitates reading the inscription.

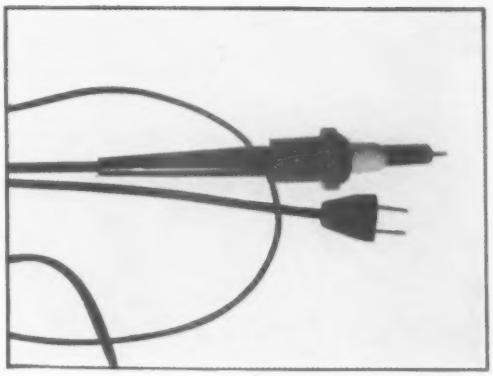

FIG. 1

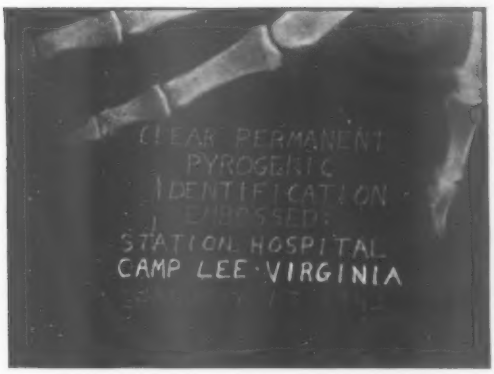
CLEAR PERMANENT
PYROGENIC
IDENTIFICATION
EMBOSSED:
STATION HOSPITAL
CAMP LEE · VIRGINIA

FIG. 2

INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

Nervous System

Nichols, B. H.: Thorotrast and diagnosis of lesions involving lower spinal canal..... 698

Dandy, W. E.: Improved localization and treatment of ruptured intervertebral disks 698

Skeletal System

Inclan, A.: Possibilities of roentgenographic study of arterial circulation in early diagnosis of bone malignancy..... 699

Miyakawa, G., and Stearns, G.: Severe osteoporosis (or osteomalacia) associated with long-continued low-grade steatorrhoea..... 699

Conley, A. H., and Miller, D. S.: Neurilemmoma of bone..... 700

Green, W. T., and Farber, S.: "Eosinophilic or solitary granuloma" of bone..... 700

Gajzago, D., and Göttche, O.: Salmonella suipestifer infections in childhood..... 701

Sternberg, W. H., and Joseph, V.: Osteodystrophia fibrosa combined with precocious puberty and exophthalmic goiter..... 701

Andersen, D. H., and Schlesinger, E. R.: Renal hyperparathyroidism with calcification of the arteries in infancy..... 702

Montfort, J. A., and Solomon, N. H.: Osteitis tuberculosa multiplex cystoides in children..... 702

Reynolds, F. W., and Wassermann, H.: Destructive osseous lesions in early syphilis 703

Key, J. A., and Large, A. M.: Histoplasmosis of the knee..... 703

Milch, H.: Epiphyseal pseudarthrosis..... 704

O'Donoghue, D. H., and Sell, L. S.: Persistent olecranon epiphyses in adults..... 704

Frost, T. T.: Multiple cystic tuberculosis of bones..... 704

Posner, I.: Sarcoidosis..... 705

Rosenberg, E. F., Dockerty, M. B., and Meyerding, H. W.: Coccidioidal arthritis 705

Stiles, G. W., and Davis, C. L.: Coccidioidal granuloma (coccidioidomycosis)..... 706

Benninghoven, C. D., and Miller, E. R.: Coccidioidal infection in bone..... 706

Bell, A. L. L., Edson, G. N., and Hornick, N.: Characteristic bone and joint changes in compressed-air workers..... 707

Brown, L. T., and Kuhns, J. G.: Extension deformities of cervical spine..... 707

Cleveland, M., and Bosworth, D. M.: Pathology of tuberculosis of spine..... 707

Simon, R. S.: Diagnosis and treatment of kyphosis dorsalis juvenilis (Scheuermann's kyphosis) in the early stage..... 708

Inman, V. T., and Saunders, J. B. deC. M.: Clinico-anatomical aspects of lumbosacral region..... 708

Pheasant, H. C., and Swenson, P. C.: Lumbosacral region..... 709

Lipscomb, P. R., and Chatterton, C. C.: Osteochondritis juvenilis of acetabulum... 709

Reed, J., and Sosman, M. C.: Gaucher's disease..... 709

Schein, A. J., and Arkin, A. M.: Hip-joint involvement in Gaucher's disease..... 709

Chont, L. K.: Roentgen sign of early suppurative arthritis of hip in infancy..... 710

Blood and Lymph System

Smith, C. H.: Mediterranean (Cooley's) anemia in youth of nineteen years observed since early childhood..... 710

Homans, J.: Thrombosis as complication of venography..... 711

Kleinberg, S.: Angioma of the foot..... 712

ROENTGEN AND RADIUM THERAPY

Goin, L. S.: Management of patients receiving therapy for cancer..... 712

Pohle, E. A., and Benson, R. R.: Roentgen therapy in cancer of the breast..... 712

O'Brien, F. W.: Place of irradiation in treatment of cancer of the breast..... 713

Budd, J. W.: Pathology of the breast..... 713

Soiland, A.: Preoperative irradiation of breast cancer..... 714

Kilgore, A. R.: Selection of cases for surgery in cancer of the breast..... 714

Lenz, M.: Roentgen therapy of cancer of the breast and regional metastases..... 714

Howes, W. E., and Bernstein, L.: Methods used and results obtained in treatment of widespread metastases secondary to mammary cancer..... 715

Cohn, L. C.: Carcinoma of female breast.... 715

Hill, R. P., and Stout, A. P.: Sarcoma of the breast..... 715

Murphy, J. B.: Analysis of trends in cancer research..... 716

Paul, L. W., and Pohle, E. A.: Radiation osteitis of ribs..... 717

Graves, R. C., and Lawrence, K. B.: Bilateral embryonal carcinoma of testicle..... 717

Herger, C. C., and Sauer, H. R.: Occurrence and clinical course of radium reactions following use of radon implants in treatment of carcinoma of the bladder..... 718

ABSTRACTS OF ROENTGEN AND RADIUM LITERATURE

ROENTGEN DIAGNOSIS

NERVOUS SYSTEM

Nichols, B. H. Thorotrast and the diagnosis of lesions involving the lower spinal canal. *Radiology*, June, 1942, *38*, 679–685.

Low back pain radiating down the leg is frequently caused by posterior protrusion of an intervertebral disc. The best method of demonstrating such lesions is by making a roentgenogram of the spine after the injection of 10 cc. thorotrast. Thorotrast is a colloidal liquid and therefore more miscible than the iodized oils and with its use the nerve roots can be identified more satisfactorily. The patient is prepared for operation before the thorotrast is injected so that operation can be performed immediately afterward if the findings indicate it. It is important to remove the thorotrast after the examination is made so that no harm may be done by its radioactive property. This is accomplished by giving 750 cc. of 45 per cent saline solution intravenously and continuing spinal drainage for ten or fifteen minutes afterward. In this way 80 to 85 per cent of the thorotrast can be recovered. Five cases are described and illustrated with roentgenograms.

In the discussion Dr. Kinney emphasized the importance of following Dr. Nichols' technique carefully. The thorotrast method should not be used by the inexperienced surgeon for it is apt to cause arachnoiditis from the retained radioactive salt. A high percentage of disability has persisted after the removal of herniated discs, and a careful study of the nerve supply in relation to pain of this type is most important.—*Audrey G. Morgan.*

Dandy, Walter E. Improved localization and treatment of ruptured intervertebral disks. *J. Am. M. Ass.*, Oct. 24, 1942, *120*, 605–607.

The author's purpose is to suggest (1) a method of localization of ruptured intervertebral discs and (2) an improved method of operative attack on the discs.

Since the diagnosis can be made with almost absolute accuracy by the clinical symptoms alone, lumbar punctures, injection of contrast mediums such as air, iodized poppyseed oil and thorotrast into the spine are entirely unnecessary. Clinically the signs and symptoms of the small so-called concealed discs are precisely like the protruding discs and the treatment is the same. All of these would be missed by intraspinal injections of contrast mediums and they now outnumber the protruding discs 3 to 2. There are only three or four other lesions that can give symptoms fairly similar to a disc, i.e. backache and sciatica (in attacks) intensified by coughing and sneezing: (1) tumors of the cauda equina, (2) congenitally defective fifth lumbar vertebra with destruction of the articular process, (3) spondylolisthesis, and (4) cancer invading the low retroperitoneal spaces. Various statistical studies show that 96 per cent of all ruptured discs are in the lumbar region, and 98 per cent of the lumbar discs are at the fourth and fifth.

The following test provides greater precision in locating the disc without exploring it: When the unilateral exposure of the spine has been made, the cutaneous incision is perhaps 4 inches long and uncovers both the fourth and fifth laminae. A periosteal elevator pushes the spines of the fourth and fifth spinous processes downward, i.e., caudally, and determines the mobility of each vertebra. The disc will be where the greater movement is shown. This test is effective because the defective disc has weakened the spinal column locally and this in turn causes mobility. It is this free play at the disc that is responsible for the intensification of the pain by coughing and sneezing. This test in over 85 per cent of the cases will correctly determine the site of the lesion.

Dandy decided that a thorough removal of the necrotic contents of a ruptured disc would hasten the postoperative period of recovery and that it was probably better to remove enough of the lining cartilage to bare the bone and permit granulations to fill the cavity. Since the introduction of this procedure three months ago he found that recovery has been consistently uneventful and it has not been necessary to reopen a wound. Because of the firm union that eventually results after the disc has healed with fibrous tissue it is clear that a fusion is entirely unnecessary.—*S. G. Henderson.*

SKELETAL SYSTEM

Inclan, Alberto. Possibilities of the roentgenographic study of the arterial circulation in the early diagnosis of bone malignancy. *J. Bone & Joint Surg.*, April, 1942, *24*, 259–269.

The author states that arteriography is of importance and practical value in the differential diagnosis of borderline lesions of bone. It will reveal and clearly determine the malignant or benign character of the lesions and it thus becomes of primary consideration in the early diagnosis of bone malignancy. The advantages of arteriography as a method for the early diagnosis of bone malignancy are dependent primarily on how early in the disease this form of investigation is undertaken. Arteriography will afford a definite diagnosis of a bone neoplasm in an accessible region when the contrast obtained by the opaque substance used is clear and the technique employed is so exact that the slightest deviation from normal in the arterial circulation is detectable.

Inclan found from both clinical and experimental work, that the use of ascending arteriography broadens the field for the employment of this method of investigation, since it may be employed when the use of descending arteriography would be impracticable or impossible. In his effort to improve upon previous methods using injection of the aorta for abdominal diagnosis, the internal carotid for cerebral angiography, etc., he developed the method of ascending arteriography in which he was able to inject against the arterial stream and obtain the filling of the arteries away from the point of injection. He reproduces an arteriogram of a dog in which the abdominal, spinal and renal circulation was visualized by injection of the femoral artery, against the normal direction of the blood stream, with pressure on the descending aorta interrupting the arterial circulation.

While the injection is being given, the roentgenologist makes three successive exposures, two of the arterial and one of the venous circulation, using the highest milliamperage possible with the greatest kilovoltage. The time of exposure must be less than one-tenth of a second. Inclan advocates the use of an extra fast Bucky diaphragm. He regards thorotrast or thorium dioxide as the best media to be used.

The ability to recognize the important changes demonstrated by this procedure depends largely on a comprehensive knowledge of the appearance of the normal arterial circulation. In the arteriogram the stroma of an osteogenic sarcoma, as well as the actual size and area of invasion, can be demonstrated in addition to the important arterial changes, whereas a simple roentgenogram shows only slight signs of a bone tumor. The most striking and characteristic arteriographic sign of bone malignancy is the filling in of the stroma of the new growth by numerous vessels, forming an erratic network and showing the extension of the invading tumor. Careful examination of the arteriogram under a magnifying glass enables one to trace the vessels and their irregular, disorderly distribution in the tumor mass. Another evidence of malignancy is the presence of new atypical arterial circulation with pedicles from the main artery and numerous irregular branches entering the bone lesion. This is an important observation, since it defines clearly the limits of the lesion. The premature appearance of very rich venous circulation, with formation of gross venous pedicles arising from the tumor and entering the neighboring vein is also an important sign. In the advanced cases, the arterial circulation is increased and appears to be distributed perpendicularly to the bone.

The technique of injection is described in full, with also a list of six errors to be avoided in using the procedure. Inclan believes the method deserves further trial, especially in institutions devoted to the study of cancer, where its real value may be ascertained.—*R. S. Bromer.*

Miyakawa, George, and Stearns, Genevieve. Severe osteoporosis (or osteomalacia) associated with long-continued low-grade steatorrhoea. *J. Bone & Joint Surg.*, April, 1942, *24*, 429–437.

A far-advanced case of osteomalaica is reported which appeared to have developed in the absence of marked dietary indiscretions. The milk intake of the patient had been ample for at least two years, but no additional vitamin D had been ingested. The patient was a female aged thirty-four. She showed a persistent elevation of fecal fat. The history indicated that some degree of steatorrhea had been present for more than ten years. It seemed probable that this mild degree of steatorrhea over so long a period was a major factor in the development of the osteomalacia. Retention of bone minerals was ample when cod-liver oil, bile-salt, and

pancreatin therapies were instituted in conjunction with the ingestion of a diet rich in calcium and phosphorus, and low in fat content.

In general, the cases in which osteomalacia develops fall into three main groups based on their etiology:

1. Pregnancy and insufficient calcium intake.
2. Starvation osteomalacia of war-torn people.
3. Idiopathic steatorrhea followed by osteomalacia.

The roentgenograms of the patient showed marked osteoporosis of the spine with compression of the vertebrae. Both ulnae showed pseudo-fractures, similar to those described by Looser in 1920. The pelvis showed the typical deformity caused by osteomalacia, and there was also marked deformity of the sternum with osteoporosis.

The authors have encountered one other patient whose spine showed far-advanced osteoporosis and whose stools showed elevated fecal fat. It is, however, too early in this second case to tell what results dietary and medical management will produce in this case. But it is possible, they state, that in a certain number of cases of so-called idiopathic osteoporosis the primary fault lies in the patient's inability to digest fat.—*R. S. Bromer.*

Conley, A. H., and Miller, D. S. Neurilemmoma of bone; case report. *J. Bone & Joint Surg.*, July, 1942, *24*, 684–689.

Primary nerve sheath tumor of bone is an extremely rare condition. The question of malignancy in this type of tumor is very important, the treatment depending upon the microscopic diagnosis of the tumor. This nerve sheath tumor has in the past been called by many names such as neurofibroma, schwannoma, perineural fibroblastoma, and peripheral neuroma. The term "neurolemmoma" used by Stout is considered quite appropriate by the authors.

A three year study of a case of this condition is reported. The neurological examination of the patient indicated, in all probability, that this was a lesion in the region of the cauda equina. This had to be differentiated from a lumbosacral lesion, and the possibility of a ruptured intervertebral disc. The roentgenogram revealed an area of rarefaction of the size of a half dollar in the upper margin of the first sacral vertebra. This had a thin cyst-like wall. During the period of observation of the patient this area became sclerosed, leaving only a small rarefied area with a mild trabeculation still present. The roentgenographic appearance of the tumor excluded the diagnoses suggested by the neurological examination.

The patient was operated upon and thereafter received roentgen therapy weekly for ten weeks.

That there was no intrinsic cauda equina tumor may be inferred from a negative spinal tap which gave no evidence of irritation.

The authors concur with De Santo and Burgess that this is a benign tumor and that excision, followed by roentgen therapy, is the treatment of choice.—*R. S. Bromer.*

Green, William T., and Farber, Sidney. "Eosinophilic or solitary granuloma" of bone. *J. Bone & Joint Surg.*, July, 1942, *24*, 499–526.

Since 1930 the authors have had the opportunity to study 13 children who suffered from a disease process characterized by either solitary or multiple destructive lesions of bone, without clinical or roentgenographic evidence of visceral disease. These lesions appeared to be identical with what has been described in the recent literature as a new disease under the name of "solitary granuloma" and "eosinophilic granuloma." On the basis of pathological studies of material which included tissue removed at operation from patients whose case histories are described in this paper, Farber concluded that these benign destructive lesions of bone do not constitute a new disease process, but represent rather one variant of a basic disease process, of which the clinical pictures known as Hand-Schüller-Christian's disease, certain forms of xanthoma, and Letterer-Siwe disease are other examples.

Ten cases are reported, all of which were in children under twelve years of age. Roentgenologically, single lesions simulated bone cyst, osteomyelitis, or malignancy. Multiple lesions suggested multiple myeloma or malignancy, but in the roentgenograms were indistinguishable from Hand-Schüller-Christian's disease. There was little general illness associated with the disease in most instances. The symptoms were attributable mainly to the local process. The histopathology presented variations from "eosinophilic granuloma" to "lipogranuloma," which is interpreted as identical with certain stages of Hand-Schüller-Christian's disease.

Ordinarily, the lesions have healed quite promptly after roentgen irradiation and, on occasion, curettage.

Pain is usually a more prominent feature in instances of Ewing's tumor than in this disease. In Ewing's tumor, also, the area of involvement as shown in the roentgenogram is usually not so circumscribed, and there is likely to be considerable subperiosteal new bone formation. Multiple punched-out defects may be found in leukemia, but these defects are usually smaller and more generalized than in this disease. Hematological study should be sufficient to exclude the diagnosis of leukemia.

Nine of the 10 patients reported in this communication were well on a follow-up examination three to ten years after they were first observed. One had died, the details of which case were unknown. Despite the excellent prognosis in 9 of 10 patients in this group in which the recognized lesions were restricted to bone, if the suggested relationship to Hand-Schüller-Christian's disease exists, the prognosis given in an individual case should be guarded, and the possibility of visceral lesions should be kept in mind.—*R. S. Bromer.*

Gajzago, Desiderius, and Göttche, Oskar. Salmonella suipestifer infections in childhood. *Am. J. Dis. Child.*, Jan., 1942, *63*, 15–29.

The literature of the last few years shows that the number of reports on infections with *Salmonella suipestifer* is increasing. The authors describe 6 cases. They were able to collect 34 cases in children including their 6 cases. Of these 14 occurred in the United States. In 17 of these 34 cases osteomyelitis developed after infection with *S. suipestifer*. The occurrence of such osteomyelitis has never been described in the case of an adult. Of the series of 34 cases, 25 were patients under two years of age.

The roentgenographic changes are much less pronounced and much less extensive than those in cases of other types of osteomyelitis. The first roentgen sign is the appearance of a slight structural disturbance under the epiphyseal line; later in this spot a cavity develops, usually a Brodie abscess no larger than a pea. The cavity generally appears during the third week of illness and is most clearly observed from the fourth to the sixth week, when the clinical condition most often shows improvement. Periosteal thickening, which is one of the most characteristic symptoms of osteomyelitis, is usually slight and may be absent; in 3 of the authors' cases there was no periosteal thickening. In the cases thus far described in the literature only metaphyses were affected, and the extension of the process into the diaphysis, with the occurrence of greater necrosis and more pronounced periosteal thickening, has not been described. Epiphysitis was observed only in their first case in which the joint was not affected. The localization of the focus is of interest. Thus far the following sites have been described: proximal metaphysis of the humerus, 13 cases; distal metaphysis of the femur, 8 cases and distal metaphysis of the tibia, 1 case. In this list, the authors counted every focus as a separate unit. In some cases the pathologic picture was similar to that of typhoid fever, paratyphus or dysentery. In other cases, in which purulent processes were present, *S. suipestifer* was isolated from the pus.

The authors state that *S. suipestifer* infection occurs much more often than was previously thought. While the subject is just now beginning to be investigated, enough data have been compiled to make further studies possible.—*R. S. Bromer.*

Sternberg, William H., and Joseph, Vera. Osteodystrophia fibrosa combined with precocious puberty and exophthalmic goiter; pathologic report of a case. *Am. J. Dis. Child.*, April, 1942, *63*, 748–783.

The authors report the pathologic observations in a case of osteodystrophia fibrosa combined with precocious puberty, melanotic pigmentation and severe exophthalmic goiter. The disease of the bones was patchy and was characterized by lacunar osteoclastic resorption, fibrosis of marrow spaces, osteoblastic repair and cyst formation. The presence of islands of cartilage with bone formation at their peripheries was looked upon as an extreme effort at repair. The pathologic picture resembled in some respects von Recklinghausen's disease, although the tempo of the bone resorption was somewhat slower and hyperparathyroidism clearly was not present.

The important endocrine findings were a hyperplastic thyroid, thymus and lymphoid structures, mature cystic ovaries with no evidence of luteinization, a narrow adrenal cortex, and parathyroids within normal limits. The pituitary gland showed basophilic hyperplasia

with adenoma formation. No significant neurologic lesion was present.

The roentgenologic as well as the pathologic evidence revealed a strikingly advanced bone age, with premature closure of the epiphyses and consequent dwarfism.

Sternberg and Joseph feel that the presence of exophthalmic goiter in their case and others of this syndrome may be suggestive in that it may furnish a clue to the complex hormonal imbalance present in these patients which probably involves the gonads, adrenals, thyroid and pituitary.—*R. S. Bromer.*

ANDERSEN, DOROTHY H., and SCHLESINGER, EDWARD R. Renal hyperparathyroidism with calcification of the arteries in infancy. *Am. J. Dis. Child.*, Jan., 1942, *63*, 102–125.

The authors describe 2 cases of renal hyperparathyroidism in infancy. The presenting clinical picture was that of tetany and acidosis, both resistant to therapy, associated with alterations in the calcium and phosphorus contents of the serum. In the first case antirachitic serum was given, which was followed by calcification of the small arteries throughout the body and death at the age of six months as the result of an infarct of the heart. The second infant was treated more conservatively and showed metastatic calcification of less severe degree. The renal insufficiency was at first inconspicuous and was characterized by urine of low specific gravity, chronic acidosis and an elevated nonprotein nitrogen content of the serum. The essential postmortem observations were a severe renal anomaly, hypertrophy of the parathyroids, osteitis fibrosa and metastatic calcification with medial calcification of the small arteries throughout the body.

The authors note that in infancy and childhood the renal lesion is congenital, but in the adult the renal insufficiency may also result from pyelonephritis, glomerulonephritis or vascular disease. At all ages the renal insufficiency is severe and fairly static. During the growth period there is greater sensitivity to variations in the calcium and vitamin D intake. Severe rickets may occur in late childhood under circumstances which do not usually produce rickets. At any age period a moderate excess of vitamin D, at levels usually harmless, may produce hypercalcification of bones and deposits of calcium in tissues, including the media of small arteries.

In their cases the changes in the bones and parathyroids were less marked than in reported cases of older children and adults. They think this might have been due to the high intake of calcium and vitamin D or to the shorter duration of the disease, or to both.

Dwarfism is found in children with renal rickets but is absent when the renal hyperparathyroidism begins after the adolescent growth period. No retardation of growth occurred in the 2 cases reported. Andersen and Schlesinger suggest tentatively that dwarfism is the result of the epiphyseal changes due to vitamin D deficiency rather than of the hyperparathyroidism itself.—*R. S. Bromer.*

MONTFORT, JOHN A., and SOLOMON, NATHANIEL H. Osteitis tuberculosa multiplex cystoides in children. *Am. J. Dis. Child.*, Feb., 1942, *63*, 346–353.

Cystic tuberculosis of bone is an uncommon form of osseous tuberculosis which rarely occurs in children. Jüngling in 1920 first reported on this disease and termed it osteitis tuberculosa multiplex cystica. In 1928 he reviewed the subject and the collected cases had the following characteristics: (1) the onset was gradual; (2) pain began early but was not severe; (3) the onset occurred during puberty or thereafter; (4) the small long bones of the hands and feet were most often affected; (5) there was a tendency to formation of large cysts without surrounding sclerosis; (6) there was no involvement of the periosteum or the joints; (7) the tuberculin test usually gave negative results; (8) tubercle bacilli were not found by stains, cultures or guinea pig inoculation; (9) microscopic examination showed epithelioid cells, rarely giant cells, and no caseation; (10) there were often associated lesions of the skin (sarcoid); (11) the course was slow, with a tendency to improvement; (12) the patient's general health usually was unimpaired.

The reported cases of this disease in children differ from Jüngling's case (adult patients) in that: (1) there was a greater tendency to involvement of long hollow bones; (2) associated cutaneous skin lesions were infrequently encountered; (3) tuberculin tests usually gave markedly positive results; (5) caseation was occasionally noted; (6) there was a tendency for the lesions to heal locally, but frequently the patient died of generalized tuberculosis shortly after they were healed. The authors suggest

that the condition in the cases reported by Jüngling resembles Boeck's sarcoid, and the osteitis tuberculosa multiplex cystica that occurs in children represents an entity which is intermediate between Boeck's sarcoid and caseous tuberculosis of bone.

The bones involved in the patient reported by the authors were the humerus, the thoracic vertebrae and the skull, circumscribed bone defects being present. The roentgenogram of the chest showed very marked widening of the mediastinal shadow especially on the right side. The patient was a Negro boy, aged sixteen months. Biopsy of the scalp and bony tissue of the skull was diagnosed as tuberculous inflammation of skin and bone and osseous necrosis.

Montfort and Solomon state that the disease must be differentiated from syphilis, nonspecific osteomyelitis, multiple myeloma, osteitis fibrosa cystica, Hand-Schüller-Christian's disease, Gaucher's disease, echinococcus cysts, coccidioidosis, leprosy, giant cell sarcoma and metastatic malignant growth.—*R. S. Bromer.*

Reynolds, Frank W., and Wassermann, Harry. Destructive osseous lesions in early syphilis. *Arch. Int. Med.*, Feb., 1942, *69*, 263–276.

The bones may be affected in early syphilis and descriptions of pain and swelling of the bones are found in the writings of many of the earliest syphilologists. This pain and swelling of the bones often overshadows the other signs of early syphilis. The pain is more severe at night than in the daytime.

The bone involvement of early syphilis is usually a proliferative periostitis. Destructive lesions such as osteitis, osteomyelitis and osteoperiostitis are rarer. Among approximately 10,000 cases of early syphilis seen at the Mayo Clinic from 1919 to 1940 only 15 such cases of destructive bone lesions were found. A tabulated report of the outstanding features of these 15 cases is given and of 15 other cases collected from the literature, together with illustrative roentgenograms.

The skull bones are most frequently affected. The fundamental process is an osteolysis with replacement by syphilitic granulation tissue. The roentgenogram is characteristic, showing irregularly circular areas of decreased density that have a motheaten appearance. If there is an associated periostitis there may be wavy periosteal markings parallel to the surface of the bone.

Destruction of bone may precede or follow the secondary eruption, or it may be the only manifestation of relapsing early syphilis.

As a rule, the bone lesions heal promptly on treatment and do not leave any sequels and the serologic reactions are reversed as promptly as in uncomplicated early syphilis. The authors have seen no cases of pathologic fracture from early syphilitic osteitis.—*Audrey G. Morgan.*

Key, J. Albert, and Large, Alfred M. Histoplasmosis of the knee. *J. Bone & Joint Surg.*, April, 1942, *24*, 281–290.

Histoplasmosis or reticulo-endothelial cytomycosis is a generalized disease which varies widely in its clinical characteristics, and is caused by the *Histoplasma capsulatum* of Darling. This organism was discovered in 1906 by Darling while he was searching for evidence of kala-azar in smears from the spleen, liver and bone marrow of all patients showing splenomegaly who came to autopsy at the Ancon Hospital. Meleny found that the disease may present one of the four following clinical pictures:

1. A systemic febrile disease similar to kala-azar, with an enlarged liver and spleen, septic temperature, anemia and leukopenia.

2. Lymph node enlargement may predominate, simulating Hodgkin's disease, leukemia, lymphosarcoma or aplastic anemia.

3. Pulmonary symptoms may predominate. The infection is often complicated by, or superimposed upon, pulmonary or generalized tuberculosis.

4. The infection may begin as a small skin lesion which may sometimes develop into a generalized ulcerative skin condition.

As far as the authors were able to determine, none of the cases presented in the literature showed any involvement of the joints or muscles. They report a case of a patient from whom the sections from the specimen of the knee joint showed the typical *Histoplasma capsulatum* of Darling. They believe this is the first reported instance in which the disease has been known to involve a joint and also because the case closely resembled tuberculosis of the knee joint and was so diagnosed until it was found that the guinea pig inoculation and the tuberculin test on the patient were negative. It was then thought to be a low grade infection of unknown origin. The limb was amputated and the correct diagnosis was arrived at only when it

was made by examination of the microscopic slides of the tissue of the knee joint. The patient also had involvement of the lungs as shown by roentgenographic examination before the amputation was performed. The administration of full doses of sulfathiazole had no effect.—*R. S. Bromer.*

Milch, Henry. Epiphyseal pseudarthrosis. *J. Bone & Joint Surg.*, July, 1942, *24*, 653–662.

Separation of epiphyses may occur as the result of trauma or as the consequence of a pathological process directly affecting the growing zone. In general, provided that excessive separation has not occurred, union, and even premature closure of the epiphyseal line, follows upon disappearance of the factors which caused the separation. Under certain circumstances, however, fusion may not take place, and a condition which may be called epiphyseal pseudarthrosis, or neoarthrosis arises.

Milch has observed epiphyseal pseudarthrosis at the hip under the following conditions:

1. After operative fusion of the hip.
2. After inflammatory ankylosis of the hip.
3. As a sequel to adolescent epiphysiolysis.

It may occur in any condition in which the capital epiphysis becomes ankylosed before closure of the epiphyseal plate occurs. Mechanically, mobility of the shaft of the femur, with respect to a relatively fixed head, is essential to the appearance of the condition. Successful therapy is based upon immobilization of the distal fragment in relation to the proximal fragment. Recognition of the condition is of paramount importance in explaining some cases of apparent failure after an attempt at operative fusion of the hip. Milch considers it not unreasonable to regard epiphyseal pseudarthrosis as a chronic form of the condition more commonly seen as adolescent epiphysiolysis.—*R. S. Bromer.*

O'Donoghue, D. H., and Sell, L. S. Persistent olecranon epiphyses in adults. *J. Bone & Joint Surg.*, July, 1942, *24*, 677–680.

The authors believe the case reported in this paper is the first on record in the American literature of a rare anomaly of the elbow joint, namely, a persistent olecranon epiphysis. They point out, too, the medicolegal significance of persistent epiphyses in areas exposed to trauma.

In the literature there appears to be a considerable degree of confusion between a true unfused olecranon epiphyseal plate, and the so-called patella cubiti. There are several references to the latter condition. Köhler makes the clearest differentiation between the two: first, true patella cubiti, embryonic in origin, consists of a completely isolated piece of bone, articulating and mobile, and truly an accessory bone; second, a simple persisting epiphysis, that is a persistent epiphyseal plate, is most commonly found on both sides and has a tendency to occur in families.

The case reported falls definitely in the second group. In the authors' case trauma called attention to the open epiphyseal plate on one side. Further roentgenograms revealed not only a persistent epiphyseal plate in the olecranon on the uninvolved arm, but also bilateral tripartite patellae. Roentgenographic study of other significant bones throughout the skeleton failed to reveal any further anomalies. The displaced epiphysis was replaced at open operation and held by a vitallium screw. In spite of the trauma to this epiphyseal plate resulting from both the fracture and the open reduction, it still remained open at the time of the roentgenographic examination, five months after operation and its appearance did not differ from that of the opposite elbow. It was not possible to examine either the patient's father or brother, in order to confirm Köhler's statement that the condition tends to occur in families.—*R. S. Bromer.*

Frost, Thomas T. Multiple cystic tuberculosis of bones. *Am. J. Dis. Child.*, June, 1942, *63*, 1132–1135.

Frost reports a case of multiple cystic tuberculosis of the bones. The patient was a Negro boy, eleven months old. He thinks this is the fourteenth case of multiple cystic tuberculous involvement of the skeleton to be reported in pediatric literature. The suggestion made by Martin and Fogel, that demonstrable lesions in the bones are caused only when local resistance has been lowered by previous injury, such as decalcification or rickets, appears to be borne out in his case. The bones showed evidence of decalcification. The roentgen examination of the skeletal system showed multiple central cystic lesions in the shafts of the long bones and in the carpals, metacarpals, tarsals, metatarsals and phalanges. There were also similar lesions

in the skull. Associated with the cystic lesions of the long bones there was definite evidence of periostitis and osteitis, with new periosteal bone laid down parallel to the shafts of the long bones.

The finding of a primary tuberculous complex with caseation in the lungs, with no evidence of healing and with hematogenous spread to other organs, indicated either poor resistance or an overwhelming infection. The nature of the tuberculous lesion and its widespread appearance throughout the viscera left little doubt that the lesions in the bones were also of tuberculous origin. The autopsy did not include the skeletal system. The patient's blood showed a positive Kline reaction which was apparently incidental, as there was no gross or microscopic evidence of syphilis, although this disease might have contributed to the demineralization seen in the roentgenograms.—*R. S. Bromer.*

Posner, I. Sarcoidosis; case report. *J. Pediat.*, April, 1942, *20*, 486–495.

Sarcoid is now defined as a rare group of inflammatory tumors composed of nodules of epithelioid cells. Synonyms are lupus pernio, sarcoid of Darier-Roussy, Boeck's sarcoid and lymphogranulomatosis of Schaumann. The name sarcoidosis implies a generalized distribution of the same pathological process.

The author presents a case of sarcoidosis in a female child, aged twenty-five months, who complained of poor appetite and weight loss. Clinically the child had a suggestive mongoloid appearance. The skin had a lemon yellow tint and the nutrition was poor. The chest showed diminished expansion on the left with dullness to percussion. The inguinal and cervical nodes were slightly enlarged, discrete and not tender. The Mantoux test was negative in a 1:1000 dilution.

Roentgenograms of the long bones showed periosteal proliferation and areas of cortical rarefaction. In some areas the continuity of the cortex was lost. The skull showed multiple small areas of porosity. The impression was that of some blood dyscrasia, probably leukemia. Roentgenograms of the chest showed increased hilar density with slight mottling in the central lung fields.

Sternal puncture smears were suggestive of lymphatic leukemia. This was considered the most likely diagnosis although xanthomatosis was considered as a possibility. The treatment was dietary plus transfusions for a severe anemia. There was a daily temperature elevation. Lymphadenopathy was slowly progressive. Biopsy of a cervical node showed chronic granulation tissue suggesting tuberculosis.

The patient died three months after the first admission. At autopsy there were many pinpoint yellowish-gray nodules throughout the lungs. The gross anatomical diagnosis was miliary tuberculosis of the lungs. Pathologically granulomas were found in the adventitia and subendothelial areas of the arterioles especially. These granulomas consisted of epithelioid cells concentrically arranged with peripheral lymphocytic infiltration. A few giant cells, not of the Langhans type, were found. Appropriate staining revealed no acid-fast bacilli. Similar granulomas were found in the liver, spleen, lymph nodes and bone marrow.

Sarcoid was considered as the more likely diagnosis due to absence of necrosis but the author admits that the differentiation between the two entities is not a clear one and that sarcoid may be a form of tuberculosis.—*R. M. Harvey.*

Rosenberg, Edward F., Dockerty, Malcolm B., and Meyerding, Henry W. Coccidioidal arthritis; report of a case in which the ankles were involved and the condition was unaffected by sulfanilamide and roentgen therapy. *Arch. Int. Med.*, Feb., 1942, *69*, 238–250.

Infection with *Coccioides immitis* is endemic in the Sacramento-San Joaquin Valley in Southern California and rare in other parts of the country. Only 3 cases have been seen at the Mayo Clinic.

The disease assumes two forms—the first a mild febrile disease known as valley fever, with malaise, sore throat and sometimes conjunctivitis and signs of bronchopneumonia. When the general condition begins to improve nodules of erythema nodosum appear. In about a third of the cases signs of arthritis develop at the same time as the erythema nodosum. The arthritis is mild and clears up without leaving any deformity.

The other form of the disease is a serious chronic granulomatous infection that in many respects resembles tuberculosis. It may affect the skin, lymph nodes, abdominal and thoracic viscera, meninges, bones and joints.

A case is described in a man of twenty-five

seen at the Mayo Clinic, in whom the ankle joints were involved. He had worked in the San Joaquin Valley for four years previous to the beginning of the disease in 1939. The disease began in May with a dry cough and symptoms similar to those of "flu." A rash appeared on his face and body which led his physician to make a diagnosis of typhus. By October the ankle joints were so painfully involved that he was unable to work. The condition suggested tuberculosis in many ways but the bilateral involvement was atypical. Tissue was excised for examination and showed *Coccidioides*.

Treatment with sulfanilamide and roentgen irradiation had no effect and when the patient was discharged November 15 his condition was essentially unchanged.

The mortality in this chronic granulomatous form of the disease is at least 50 per cent. The disease becomes generalized and a septic fever develops, with chills, emaciation and marked anemia. There is no specific treatment.—*Audrey G. Morgan.*

Stiles, George W., and Davis, Charles L. Coccidioidal granuloma (coccidioidomycosis). *J. Am. M. Ass.*, July 4, 1942, *119*, 765–769.

A highly fatal disease in man known as coccidioidal granuloma was recognized for many years in central California, while in the same locality a nonfatal influenza-like disease existed also and was known locally as "valley fever," "desert fever," "desert rheumatism," or "San Joaquin Valley fever." In 1936 Dickson and Gifford showed that the two maladies were caused by the same organism, *Coccidioides immitis*. In its initial stage "valley fever" resembles influenza followed in a few days by the eruptive phase of erythema nodosum in about 5 per cent of the cases, and less frequently by erythema multiforme. The cutaneous lesions are often associated with arthritis, sore throat and conjunctivitis. Coccidioidal granuloma in human beings is a chronic, progressive, highly fatal fungous disease affecting the lungs, skin, lymph nodes, bones, meninges, thoracic viscera and other body tissues. Frequently it may be mistaken for tuberculosis; however, the exclusion of acid-fast organisms and the recovery of the fungus from the sputum or body tissues should verify the diagnosis.

Pulmonary infection may be acquired by inhalation of the vegetative phase of dust laden chlamydospores. Abrasion of the skin may be a route of infection, and in rare instances the disease may be acquired by the gastrointestinal tract.

Although most of the reported cases have been found to originate in California, particularly in the San Joaquin Valley, many have also been reported from other areas—Arizona, Colorado, Illinois, Kansas, Louisiana, Missouri, Nebraska, New Mexico, Pennsylvania, South Carolina, Tennessee, Texas, Washington, Alaska, Hawaii, Old Mexico, South America and Italy.

While the greatest interest in coccidioidal infections has centered in human medicine, the veterinary phase of the problem has its place in relation to public health and animal welfare. A variety of animals may be sources of coccidioides infection. Animals in which the disease has been found include rodents, dogs, cats, sheep and cattle. A summary of the data now at hand shows a total of 116 definitely diagnosed cases of bovine coccidioidal granuloma in the United States. However, it is probable that many more cases in cattle have escaped identification or were not submitted for laboratory confirmation. Cattle affected with coccidioidal granuloma show no clinical symptoms and the lesions thus far observed have been confined to the thoracic lymph nodes and the lungs and are detected only when the animals come to slaughter.

The authors give a complete description of the gross and microscopic findings in the bovine form of the disease.—*S. G. Henderson.*

Benninghoven, Carl D., and Miller, Earl R. Coccidioidal infection in bone. *Radiology*, June, 1942, *38*, 663–666.

During the last forty years about 500 cases of coccidioidosis have been reported to the California State Department of Health. This disease enters the body through the respiratory tract and the primary stage resembles a mild influenza. The secondary stage is one of chronic granuloma which may involve the bones. The bone lesions may be unilocular or multilocular cyst-like areas, marginal erosion, destruction with periosteal new bone formation or lesions resembling osteomyelitis. There may be two different types of joint involvement, one purely synovial and the other synovial with subarticular destruction which cannot be differentiated from that of tuberculosis. The lesions are generally multiple and the bones most frequently

involved are those of the spine, pelvis, hands, feet and the bones adjacent to the knee and ankle. The epiphyseal cartilage does not act as a barrier to the spread of the infection. Soft tissue abscesses are common; they may originate in the soft tissues and extend to bone or they may result from erosion of destructive bone lesions through the cortex to the soft tissues. The mortality of the disease in the secondary stage is about 60 per cent.—*Audrey G. Morgan.*

Bell, A. L. L., Edson, George N., and Hornick, Newton. Characteristic bone and joint changes in compressed-air workers; survey of symptomless cases. *Radiology*, June, 1942, *38*, 698–707.

There have been many attempts to explain the symptoms that occur in caisson workers on transition from high to low atmospheric pressure. There are three chief theories: first that they are caused by exhaustion and cold, second by mechanical congestion, and third the recent theory of gas embolism.

The authors made a roentgen study of 32 compressed-air workers who had worked in compressed air intermittently for from three to thirty-three years. The shortest continuous period of employment was ten months and the longest thirty-six months. Of these 14 (44 per cent) had a history of bends and 4 who had not had bends had had attacks of arthritis.

The changes found in the bones are illustrated by roentgenograms. They were of three degrees: (1) necrosis without calcification; (2) necrosis with early calcification, and (3) marked calcification. Twenty-four of the patients, or 75 per cent, showed positive changes in one or more bones. In 16 of these cases the changes were in both shaft and head, in 6 there were changes in the shaft but none in the head and in only 2 there were changes in the head but none in the shaft. The bones involved were the long bones of the limbs. The bones are involved in direct proportion to their fat marrow content and their severity is in proportion to the length of continuous employment. The changes are probably caused by frequent inadequate decompressions resulting in accumulations of nitrogen and consequent infarction.

Further studies should be made on larger groups of workers and also on animals in an effort to learn more about the cause and prevention of these changes.—*Audrey G. Morgan.*

Brown, Lloyd T., and Kuhns, John G. Extension deformities of the cervical spine. *J. Bone & Joint Surg.*, April, 1942, *24*, 329–340.

The authors state the object of their paper is to show that extension deformities of the cervical spine and other remote factors can cause symptoms found in the so-called scalenus syndrome and in cervical ribs; also, that the distribution of the symptoms will depend, among other factors, upon the location of the habitual position of extreme extension of the cervical spine. If the apex of the curve is in the upper cervical region, the distribution will be through the cervical nerve plexus; and, if in the lower cervical spine, the distribution will be through the brachial plexus.

Brown and Kuhns define an extension deformity as a relatively fixed position of the joints, muscles, and ligaments, from which, if further motion is made increasing the deformity, strain or injury will occur. If the spine is in a position of full extension, further extension will cause injury, usually at the position of greatest extension or at some compensatory point. The amount of injury will depend on the anatomical structure of the injured part and its habitual position of use, combined with the habitual position of use and the anatomical structure of the rest of the body.

The anatomy of the cervical spine is discussed in detail, and 3 cases are reported. These patients had a symptomatology which suggested a cervical rib or a contracted scalenus anterior but which the authors believe was due to the neurological or vascular irritation from an extension deformity of the cervical spine. In their experience, the correction of this deformity combined with the correction of the faulty use of the body as a whole will bring relief of the neurological as well as of the vascular symptoms in a majority of cases without the necessity of operative procedure.—*R. S. Bromer.*

Cleveland, Mather, and Bosworth, David M. Pathology of tuberculosis of the spine. *J. Bone & Joint Surg.*, July, 1942, *24*, 527–546.

For the past six years, the authors state, they have been investigating all available material to determine, if possible, the localization, type, and method of invasion of tuberculosis of the adult human spine. As a result of their studies, they conclude that two pathological processes

are encountered in the human spine due to tuberculosis; first, caseation of bone and soft tissue—a destructive lesion due directly to the infection—and second, sclerosis of the bone, which they believe is a vascular phenomenon occasioned by loss of blood supply from thrombosis or endarteritis, or occlusion or destruction of blood vessels by the presence of large dissecting abscesses. They conclude, too, that the roentgenogram will often fail to reveal the presence of tuberculosis of the spine, and will never reveal the full extent of the damage due to the disease. They have searched in vain for roentgenographic evidence of tuberculosis in many spines which have been massively invaded, and where postmortem examination has yielded abundant evidence of the disease. There are certain roentgenographic findings previously overlooked which they now recognize—such as sclerosis or mottling of the vertebral bodies in a known tuberculous patient—which lead to an earlier diagnosis of the disease than was formerly possible.

Cleveland and Bosworth, too, could not find evidence to support the belief that the tuberculous lesion begins in the intervertebral disc. Since the main intervertebral joint is not diarthrodial and is therefore without a capsule or synovial lining, and has no blood vessels, the ordinary implantation of tubercle bacillus infection, as an embolic process, cannot apply to the intervertebral disc. The lesion must therefore begin in the bone or in the surrounding soft tissue which has an adequate blood supply. The disease may begin in the diarthrodial joints posteriorly, but this is not so frequently seen.—*R. S. Bromer.*

Simon, Robert S. Diagnosis and treatment of kyphosis dorsalis juvenilis (Scheuermann's kyphosis) in the early stage. *J. Bone & Joint Surg.*, July, 1942, *24*, 681–683.

Kyphosis dorsalis juvenilis (Scheuermann's kyphosis) may be seen between the ages of fifteen and twenty-two years, but it may begin as early as eight or ten years of age. Following the theory of Schneider that there is some relationship between the diseases of the epiphysis and vitamin A deficiency, the eyes of all children with this condition were examined for hemeralopia and xerophthalmia. It was found that most of the children with kyphosis dorsalis juvenilis suffered from slight hemeralopia, and xerophthalmia was found in 2 of the group from nine to thirteen years of age. In a parallel group of children with poor posture only, practically no hemeralopia was found, and no child with xerophthalmia.

The blood serum of these children was examined for carotene beta and vitamin A, and it was found that most of the children with juvenile kyphosis showed a lack or deficiency of vitamin A. Simon believes that inasmuch as roentgenographic examination of such young patients never shows the pronounced symptoms of the disease, the proof of vitamin A deficiency is an important aid in early diagnosis. Moreover, if vitamin A deficiency exists in older patients, it demonstrates that the active period of the disease has not passed.

Treatment of kyphosis dorsalis juvenilis in the early stage of the disease is based primarily on rest for the diseased spine. This is obtained by a plaster of paris corset, which is worn for six months; wearing this corset, it is possible for the child to attend school. In addition, the child is given 40,000 international units of vitamin A daily for three months.—*R. S. Bromer.*

Inman, Verne T., and Saunders, John B. deC. M. Clinicoanatomical aspects of the lumbosacral region. *Radiology*, June, 1942, *38*, 669–678.

The authors call attention to the inaccuracy of the name sciatica for the many cases of low back pain, in which the sciatic nerve may or may not be involved. They give a detailed discussion of the anatomy, particularly the innervation of the lumbosacral region, and conclude that many of these cases of low back pain are caused by herniation of the intervertebral discs and injuries of the ligamentum flavum. High tribute is paid to the roentgenologist in the diagnosis of these cases but it is felt that greater technical delicacy is required to demonstrate spinal processes, and that further aid in diagnosis will be furnished by closer observation of the points of attachment of the muscles and ligaments to the skeleton. Reliance must be placed primarily on the roentgenogram to determine whether laminectomy is indicated in lesions of the intervertebral disc and ligamentum flavum. Even after laminectomy, however, pain often persists in these cases which tends to show that the roentgenologist must not confine his attention to the intervertebral discs and ligaments but must also look for evidence of associated involvement of the bones.—*Audrey G. Morgan.*

Pheasant, Homer C., and Swenson, Paul C. The lumbosacral region; correlation of roentgenographic and anatomical observations. *J. Bone & Joint Surg.*, April, 1942, *24*, 299–306.

This paper is an attempt to correlate the roentgenographic and anatomical findings at the lumbosacral junction by careful comparison with dissected specimens. Besides the statistical data which are presented, the authors draw attention to two interesting findings. The first was that the degree of osteo-arthritis present in a given case is always a great deal more advanced than the roentgenograms would indicate, particularly as far as the posterior elements of the vertebral segments are concerned. The second was that there are confusing findings in the roentgenograms which at times, because of the varying projection of the central roentgen-ray beam and the asymmetrical development of the articular processes, will produce an appearance suggestive of failure of fusion, but in reality the segments will be found quite intact.

The variations in the anatomical structure are briefly discussed. The oblique, coronal (curved) plane is regarded as perhaps the most desirable for the human lumbosacral articulations, and the approach to the coronal plane should be considered the "evolutionary normal."—*R. S. Bromer.*

Lipscomb, Paul R., and Chatterton, Carl C. Osteochondritis juvenilis of the acetabulum. *J. Bone & Joint Surg.*, April, 1942, *24*, 372–381.

The authors report 5 cases of osteochondritis juvenilis affecting the acetabulum. The literature presents comparatively little concerning this condition. Only 1 case has been reported previously in which the acetabulum was involved without changes in the corresponding epiphysis of the femoral head. In 3 of their cases, the acetabula were involved without changes detectable roentgenographically in the femoral epiphyses. In 2 cases other centers of ossification were involved.

Osteochondritis juvenilis of the acetabulum may affect the primary centers of ossification or it may involve the secondary centers. The change is most likely to occur at the superior rim or surface of the acetabulum. Treatment is conservative and should be directed toward relief of strain which results from weight bearing on the involved region. In 2 of their cases in which healing occurred there was little, if any, remaining deformity.—*R. S. Bromer.*

Reed, James, and Sosman, Merrill C. Gaucher's disease. *Radiology*, May, 1942, *38*, 579–583.

Gaucher's disease is a disturbance of cell metabolism in the reticulo-endothelial cells and histiocytes. There is enlargement of the spleen, liver and sometimes the lymph nodes, thrombocytopenia and often leukopenia. The changes seen in the bones may be confused with those of osteomyelitis but no organisms can be found in the pus. The intervertebral discs are normal, which differentiates this condition from tuberculosis.

A case is described in a girl of twenty-one in whom the bone findings were atypical and the spleen was not enlarged on palpation. She had been operated on twice for osteomyelitis. The clinical picture resembled that of rheumatic fever and the bone changes those of rheumatoid arthritis. When she came under the care of the authors a roentgen examination showed the spleen and liver enlarged. This suggested the possibility of Gaucher's disease and sections of an excised piece of bone showed typical Gaucher cells.

In this case the heart was enlarged and the atrioventricular conduction time slowed. It is possible that this was caused by the presence of Gaucher cells in the myocardium. The disease is generally familial but examination of the members of the family of this patient did not show any other cases.—*Audrey G. Morgan.*

Schein, Albert J., and Arkin, Alvin M. Hip-joint involvement in Gaucher's disease. *J. Bone & Joint Surg.*, April, 1942, *24*, 396–410.

Gaucher's disease was first described in 1882 by a man who gave his name to the condition. He thought it was a neoplasm. Subsequently, it was found to be a rare, familial disorder of lipoid metabolism, characterized by the deposition of kerasin in the reticulum cells of the reticulo-endothelial system. These cells take on a typical appearance, and are called Gaucher cells. The disease is largely, though not entirely, confined to the Jewish race. Symptoms occur most often in childhood and adolescence, but, because of its chronicity and slow progression, its victims may live a fairly normal life for many years. Any part of the reticulo-endothelial system may be involved, but the spleen, liver,

lymph nodes and bone marrow are most commonly affected. The bone changes were first described from the gross pathological viewpoint comparatively recently (1922) by Pick.

The authors' purpose in this paper is to review and attempt to classify the bone changes as they involve the hip joint and to add 8 additional cases. All the skeletal changes are attributable to the infiltration and replacement of the bone trabeculae by kerasin-bearing, reticulum cells. These lesions appear as translucent or more radiotransparent areas, and account for the characteristic mottling. The fusiform expansion of the lower femur with thinning of the cortex was first described by Welt, Rosenthal and Oppenheimer as typical of Gaucher's disease.

The authors' cases (as well as those from the literature) have been classified into the following groups:

A. Hip Lesions in Children
   1. Lesions of the femoral head, usually suggesting Legg-Perthes' disease or early tuberculous coxitis.
   2. Lesions of the femoral neck with:
      a. Simple infiltrative roentgenographic changes
      b. Pathological fracture of the neck
      c. Coxa vara deformity, with broadening and irregularity of the epiphyseal line, suggesting epiphysiolysis, which might be secondary to simple infiltrative changes or pathological fractures of the neck.

B. Hip Lesions in Adults
   1. Osteo-arthritic symptoms and signs, probably secondary to childhood lesions of any of the above types.
   2. Roentgenographic evidence of similar changes in patients with Gaucher's disease, usually in young adults, but without any symptoms or signs pointing to the hip. It seems likely that, in time, this group may develop symptoms of osteo-arthritis.

Although the onset is often associated with intermittent pain in various bones and joints, and low grade fever, the diagnosis can be made only by recognizing the underlying Gaucher's disease, as well as the local condition. The presence of splenomegalia, hepatomegalia, secondary anemia, often with slight leukopenia and thrombocytopenia, hemorrhages and brown pigmentation of the skin, is of importance. The findings of the typical cells confirms the diagnosis. Aspiration of the spleen and splenectomy are both unnecessary. Roentgenographic changes in the lower femora are also typical.

The paper is well illustrated showing roentgenograms of the hip lesions and also of the typical changes in the lower femora and in one case those found in the spine. The authors believe, from their study of these 8 cases, that treatment by prolonged rest is indicated to minimize deformity in the patient in the younger age group.—*R. S. Bromer.*

Chont, L. K. Roentgen sign of early suppurative arthritis of the hip in infancy. *Radiology*, June, 1942, *38*, 708–714.

Arthritis of the hip in infancy is caused by pyogenic organisms and may follow mild infections in other parts of the body. The author has had 6 cases, which are described and illustrated by roentgenograms. Three of them followed infections of the respiratory tract, a bronchitis, a lobar pneumonia and a bronchopneumonia, one followed a pneumococcus meningitis, one a furuncle and in one there was no history of previous illness.

If these cases are not treated promptly permanent crippling of the child will result. Because of the shallow and almost rimless acetabulum in the infant the head of the femur is pushed outward and upward. This is clearly shown on the roentgenogram which also shows the extent of the disease and the approximate amount of intracapsular fluid. It also differentiates an infectious arthritis from an allergic one as the roentgen findings are negative in the latter. To get reliable roentgenograms the child should lie flat on his back and the tube be centered in the midline. Both hips should be shown for purposes of comparison.—*Audrey G. Morgan.*

BLOOD AND LYMPH SYSTEM

Smith, Carl H. Mediterranean (Cooley's) anemia in a youth of nineteen years observed since early childhood. *J. Pediat.*, March, 1942, *20*, 370–382.

Previous cases of Cooley's anemia have been described with early onset, rapid downhill progression and early fatal outcome. However, a milder form exists which is usually not recognized until after infancy. This type has a more

favorable prognosis. These cases appear to be carriers of the disease and the recognition of their presence thus becomes of extreme importance.

The author reports a case in a boy, aged nineteen, who had been followed since the age of four. He had a yellowish pallor, a heart murmur, a palpable liver and spleen. His blood count showed 3 per cent nucleated red cells, 11 per cent reticulocytes, a red count of 3,700,000 and a hemoglobin of 8.5 grams per 100 cc. of blood. During the period of observation frequent readmissions were necessary at which times transfusions were given. The blood picture was typical of Cooley's anemia.

Roentgenograms revealed widened diploic spaces in the skull with mottling and osteoporosis. No perpendicular striations were seen. The bones about the elbow joint showed trabecular atrophy with coarse reticulation and striation.

A brother of the patient also had typical Cooley's anemia with similar changes in the roentgenograms of the skull and elbows. A second brother and both parents showed definite abnormalities in the red blood cells but no typical roentgen changes.

These cases prove the occurrence of a milder form of Cooley's anemia than the one customarily encountered. In these cases the disease appears late in childhood and the life expectancy is greater. They should be discovered earlier through the presence of incipient changes in the blood.

The presence of blood changes in all members of the family suggests that the trait is inherited as a dominant, which Cooley believed. Individuals possessing these changes in the blood are carriers of the disease and represent the source of inheritance.—*R. M. Harvey.*

Homans, John. Thrombosis as a complication of venography. *J. Am. M. Ass.*, May 9, 1942, *119*, 136.

This is a case report of an instance of severe pain and local thrombosis, resulting from the introduction of a 50 per cent compound diodrast solution into the lesser saphenous vein of the leg. The patient's father had died of pulmonary embolism, and a brother had suffered a serious postoperative embolic accident from which he recovered. During the previous year the patient had experienced three attacks of acute pleuritic pain, each followed after a few days by the expectoration of a moderate amount of blood. Roentgenologic study of the chest on several occasions revealed what appeared to be pulmonary infarcts. Physical examination showed no abnormalities except that forced dorsiflexion of the right foot excited a very slight discomfort high up in the back of the calf—a positive "dorsiflexion sign" which was thought to mean that thrombosis had recently occurred in some of the great venous plexuses among the large flat muscles of the calf.

It was thought advisable to make a venogram. Twenty cubic centimeters of a 50 per cent compound diodrast solution was injected over a period of twenty seconds, after which 20 cc. of salt solution was injected through the same cannula. Late in the night the patient experienced an aching discomfort in the right calf. In the morning it was clear that a fresh, extensive thrombosis had occurred in the deep veins of this leg. The venogram had given no evidence of occlusion of the veins but did show slight irregularity in the lower part of the femoral vein as if a non-occluding thrombus had previously been organized and had left several small irregularities in the wall of the vein. Because of the unexpected thrombosis, the recent pulmonary infarctions and the patient's family history, it seemed advisable to divide the femoral vein at the groin in order to head off a further spread of the thrombosis and possible detachment of an embolus. On examination of the thigh at the end of the operation it was realized that the thrombosis in the saphenous vein had progressed upward so rapidly that it had reached a point within 2 to 3 cm. of the saphenous opening. Accordingly the great saphenous vein as well was sectioned.

There was no question of any constitutional reaction, for no change in the circulatory or the nervous system occurred and urticaria or edema did not follow the introduction of the solution. It must therefore be supposed that in a person susceptible to thrombosis the introduction of a 50 per cent compound diodrast solution into the lesser saphenous vein caused immediate vasoconstriction followed by thrombosis. Even twenty-seven days after the original injection of diodrast the tendency to thrombosis was still present (because there was recurrence in the vein into which the injection had been made after extraction of an infected tooth).

The procedure is so valuable that one unfortunate but not serious accident should not be held against it.—*S. G. Henderson.*

Kleinberg, Samuel. Angioma of the foot. *J. Bone & Joint Surg.*, April, 1942, *24*, 367–371.

Kleinberg reports a case of benign capillary hemangioma of the foot, involving the cuboid and the external cuneiform bones and the soft tissue in the sole of the foot. There was undoubted vascular communication between the lesion in the bones and that in the plantar area. It was not possible to state in which of these areas the angioma began. Perhaps, as in other cases with multiple lesions, the angioma appeared in the various areas simultaneously. The patient was nineteen years old, but the growth evidently started many years previously, in childhood. While, it had periodically caused symptoms, these were not severe until shortly before she was seen by the author when, because of marked pain and disability, she was compelled to seek relief.

The roentgenograms showed an extensive destructive lesion in the cuboid and external cuneiform bones. In the cuboid the inner two-thirds was involved and in the cuneiform the entire bone was involved. The osseous tissue was replaced by cystic areas which varied in size and shape and which were surrounded by narrow walls of bone of lesser or greater density. In some areas the trabeculae of bone were very sclerotic. The other bones of the foot appeared to be underdeveloped, especially the metatarsals. The patient was operated upon, healing progressed very slowly and the swelling of the foot persisted for a long time but at the present time the patient has no symptoms and is apparently cured.—*R. S. Bromer.*

ROENTGEN AND RADIUM THERAPY

Goin, Lowell S. The management of patients receiving radiation therapy for cancer. *Radiology*, May, 1942, *38*, 513–515.

The author emphasizes the importance in radiology of considering the patient as an individual, and not simply treating the disease with certain physical factors of radiation. He advocates telling the patient the truth about the disease and enlisting his cooperation rather than giving him evasive replies and stimulating fear.

Many patients with cancer are in a run down condition when they come for treatment as a result either of the disease or of ill-advised efforts to treat it with vegetarian diet, fruit juices, etc. They should be treated with vitamins, high calory diet and adequate treatment for anemia before irradiation is begun. If irradiation sickness occurs it may be treated with liver extract. The patient should also be encouraged to take large amounts of glucose which may be given in the form of corn syrup. It may be given intravenously by the drip method if necessary. Menopausal symptoms following irradiation of the pelvis may be treated with one of the estrogens. Dryness of the mouth and loss of taste may be controlled fairly well with large doses of thiamin chloride. Treatment may be followed by cystitis, proctitis or adhesive vaginitis. The latter may be treated by dilatation and packing with vaseline gauze. Cystitis may be controlled by drinking large amounts of water and fruit juices. Small retention enemata of olive oil or cornstarch are useful in proctitis.

Increased attention to such details will improve the results of treatment.—*Audrey G. Morgan.*

Pohle, Ernst A., and Benson, Roland R. Roentgen therapy in cancer of the breast. *Radiology*, May, 1942, *38*, 516–523.

This article from the Department of Radiology of the State of Wisconsin General Hospital gives the technique used in preoperative and postoperative treatment, in inoperable cases and for recurrences and metastases. The treatment of complications and late sequels of treatment is also discussed.

In 1935 this Department gave postoperative irradiation to 42 patients, 17 of whom had had no evidence of metastasis at the time of operation while 25 showed involvement of the axillary lymph nodes. In 1937 there were 41 patients, 18 without and 23 with metastasis. Among the 1935 group, 70.6 per cent of the patients free from metastasis on operation were living and free of recurrence after three years, but this was true of only 36 per cent of the patients who had had metastasis. The figure for the whole group was 50 per cent. The corresponding figures for 1937 were 55.6, 43.5 and 48.8 per cent. The combined rates for the two years—50 and 48.8 per cent—were almost the same. The five year figures are 53 per cent living and well for those without metastasis and 28 per cent for those with metastasis, a combined figure of 38.1 per cent. These figures are based

on the assumption that all patients who disappeared had died of cancer. Two patients were untraced from the 1935 group and 4 from the 1937 group.

In 1935, 28 cases and in 1937, 42 cases were treated for metastasis following operation for cancer of the breast. Satisfactory relief was obtained in 64.3 per cent of the first group and 69.2 per cent of the second. Thorough follow-up and re-examination about every six months is very important in these cases.—*Audrey G. Morgan.*

O'Brien, Frederick W. Place of irradiation in the treatment of cancer of the breast. *Radiology*, May, 1942, *38*, 524–532.

The author believes that irradiation without surgery should not be used in cases of cancer of the breast which with surgery give a five year cure rate of 70 per cent or better. He emphasizes the distinction between a five year survival rate (patient alive but with recurrence) and a five year cure rate (patient alive and free of disease). This includes only Stage I cases. As soon as the disease has extended to the axilla the surgical five year cure rate drops to about 30 per cent. If operation is performed it should be a radical mastectomy, for in 30 per cent of the cases classified as early the axillary lymph nodes are invaded. Roentgen examination of the chest, spine and pelvis should be made before operation no matter how small the primary tumors. Such examination often shows metastatic foci in the bones.

Preoperative irradiation is of value in immobilizing very malignant tumors and improving the cure rate in this group. There is no evidence that preoperative irradiation stimulates tumor growth but there is abundant clinical and experimental evidence that it halts it. In CII cases preoperative irradiation is indicated as a means of differentiating between inflammatory and carcinomatous nodules. Optimum spacing of the dose is of great importance here.

Postoperative irradiation does not seem necessary in tumors limited to the breast except in Stage III. In such cases with high malignancy, Graves reported 70 per cent five year cures in cases given postoperative irradiation as compared with 35 per cent in non-irradiated cases. Postoperative irradiation is valuable in cases in which the cancer appears clinically to be localized in the breast but pathological examination shows that it has extended to the axillary lymph nodes. In a group classified as CI PII, 39 per cent lived over five years after postoperative irradiation without demonstrable disease. In CII PII cases in which inadequate operation has been performed because it is considered only palliative postoperative irradiation is valuable. In 50 such cases seen by the author 29 treated by surgery alone lived on an average only nine months, while 20 who were given postoperative irradiation lived on the average over three years.

In recurrent and inoperable breast cancer, irradiation prolongs life and increases comfort in some cases. The advisability of roentgen castration in women over fifty, who are still menstruating, for the purpose of preventing cancer is discussed. The definite place of irradiation in the treatment of cancer of the breast has not yet been determined.—*Audrey G. Morgan.*

Budd, John W. Pathology of the breast. *Radiology*, May, 1942, *38*, 533–536.

Diseases of the breast are benign or malignant. Benign processes are known as hyperplasia, malignant ones as neoplasia. It is hard to draw a definite boundary line between them but it is probable that a process is hyperplastic as long as the two layers of epithelium grow in their normal relationship. When growth continues with a single type of cell neoplasia has begun. From a structural point of view malignant proliferation is a direct continuation from benign hyperplasia. The point of transition has not been definitely seen in human material.

In the early stage cancer is intramural and is limited by the intact basement membrane. In this stage there are few symptoms and there may not be a palpable tumor. Intra-epithelial invasion may extend to the nipple and cause the picture of Paget's disease. When the cancer cells break through the basement membrane and invade the interstitial tissues the clinical picture of cancer develops. It is unfortunate that only about 2 per cent of cases of cancer of the breast are seen in the localized stage. In prognosis the anatomical type of the cancer seems to be of less importance than the extent of the disease. The resistance of the host's tissues also affects prognosis.—*Audrey G. Morgan.*

Soiland, Albert. Preoperative irradiation of breast cancer. *Radiology*, May, 1942, *38*, 537–539.

There has been a great deal of dispute in regard to the value of preoperative and postoperative irradiation in cancer of the breast. The author, who is Director of the Los Angeles Tumor Institute, believes that, while in operable cancer irradiation alone may not give as many successful five year results as surgery alone, preoperative irradiation plus surgery has given better results than any other method of treatment. Postoperative irradiation is generally only a palliative measure in local recurrences.

In radiation therapy the field must be completely sterilized, that is, all cancer cells must be killed. The very high voltages he believes have not given any better results than those of 500 to 600 kv.

Tables are given showing the results of preoperative irradiation and surgery and irradiation alone in 63 operable cases of cancer of the breast in Stage I and 120 in Stage II. Thirty per cent is the accepted five year recovery rate for patients treated by surgery alone, while these cases of preoperative irradiation and surgery show a five year survival rate of 47 per cent. It seems too bad that of 3,400 cases of cancer of the breast in their files only 233 have been referred for preoperative irradiation. —*Audrey G. Morgan.*

Kilgore, Alson R. Selection of cases for surgery in cancer of the breast. *Radiology*, May, 1942, *38*, 540–542.

The choice between surgery and irradiation should be made in the beginning of treatment of a cancer of the breast. The author, as a surgeon, does not attempt to evaluate preoperative and postoperative irradiation in surgical cases but considers only what cases should be selected for surgery. In cases in which the cancer is limited to the breast, surgery gives about 70 per cent cure; if only one lymph node is invaded cure is about 20 per cent but if there is a chain of metastases only about 5 per cent are cured. Unfortunately it is not always easy to demonstrate metastases clinically. But if a node is more than 2 cm. in diameter it is rarely innocent and rarely the only one involved. Surgery is not indicated in such cases, nor should it be performed in cases with orange-peel skin, fixation of the tumor to the chest wall, supraclavicular edema, or demonstrable metastases in the neck or distant metastases. The size of the primary tumor in the breast is relatively unimportant. If the case is one for irradiation, surgery should not be done as the patient should not be subjected to two major procedures instead of one.

Simple mastectomy is rarely indicated. If surgery is indicated at all it should be radical. —*Audrey G. Morgan.*

Lenz, Maurice. Roentgen therapy of cancer of the breast and regional metastases: preoperative and non-operated cases. *Radiology*, June, 1942, *38*, 686–697.

Operation alone gives five year cure rates of about 70 per cent when the cancer is limited to the breast and only about 20 per cent when it has spread to the axilla. Further study of the value of preoperative and postoperative irradiation is therefore indicated.

The author studied the histories of 82 patients with cancer of the breast treated in the Radiotherapy Department of the Presbyterian Hospital, New York, between 1933 and 1937. Of these, 44 were treated by roentgen rays alone while in 38 irradiation was followed by mastectomy, radical in 37, simple in one. Final conclusions cannot be based on so small a number of cases but the findings are suggestive.

Technical factors: 200 kv., 25 ma., filtration 1 to 2 mm. copper plus 1 mm. aluminum, target-skin distance 50 cm. The breast was irradiated through four fields and the axilla through three, the total dose to the breast being approximately 8,000 r/o and to the axilla 6,000 r/o given in six to eight weeks.

About twice as many of the well differentiated tumors underwent retrogression under irradiation as of the poorly differentiated ones. The degree of retrogression, however, did not run parallel either to the histopathological type of the tumor or to the size of the dose. The author makes a distinction between radio sensitivity and radiocurability and insists that this distinction should be observed in comparing different series of cases. Both gross and microscopic examination showed a greater degree of regression in small tumors than in large ones. No definite relationship could be demonstrated between the radiosensitiveness of the tumor and its histopathological character or between its response and the size of the dose. The breast tumors responded to irradiation to a greater degree than the tumors of the axilla but com-

plete destruction of the tumor was not seen in any of the cases. In some cases only a few badly damaged cancer cells could be found. The number of five year survivals was greater in the cases treated by irradiation followed by mastectomy than is generally reported in groups treated by surgery alone. Survival was greater when the growth of the tumor was slow than when it was rapid.

The author prefers preoperative to postoperative irradiation.

In the discussion Dr. Portmann referred to the recommendation of Dr. Lenz that preoperative irradiaton should be given in borderline cases between Groups II and III. He said it would be hard to make this selection on the basis of clinical findings. He agreed that cases of cancer of the breast should be classified according to the extent of the disease in determining treatment and that advanced cases should be treated by irradiation alone.

Dr. Skinner said that, as a completely lethal dose cannot be given to cancer of the breast, it is better to use small fields limited to the area involved. In this way large doses can be given at weekly intervals without injuring the skin.—*Audrey G. Morgan.*

Howes, William E., and Bernstein, Louis. Methods used and results obtained in treatment of widespread metastases secondary to mammary cancer. *Radiology*, May, 1942, *38*, 562–572.

It has long been considered practically useless to attempt any treatment of metastasis after operation for cancer of the breast. But the authors' experience at the Brooklyn Cancer Institute has shown that much can be accomplished for these patients by irradiation. Details of the roentgen treatment in 124 such cases are given and tables showing the results. Two of the cases are described. The average length of survival in the 83 cases treated adequately was twenty months. It is estimated that without treatment the average survival is five months. Not only is life lengthened but the patients are made much more comfortable and happier by the relief of pain. When the metastases are in bone, fractures are healed and there is new bone formation and recalcification. Skin metastases can be cured and visceral metastases, except those in the liver, can be improved.—*Audrey G. Morgan.*

Cohn, L. Clarence. Carcinoma of the female breast; an analysis of the end results after five years in one hundred and ninety-two cases, with special consideration of preoperative irradiation. *Arch. Surg.*, April, 1942, *44*, 715–722.

In an earlier article the author studied 192 cases of carcinoma of the female breast in which preoperative irradiation was used, with the object of determining the value of such irradiation. It is now more than five years since the treatment was given and he reviews the cases again in an effort to settle this question.

Among 94 cases subjected to radical operation the percentage of five year cures was 45. Among the 51 cases in which treatment was entirely surgical there were 35 per cent five year cures, while in the 43 cases in which preoperative irradiation was used the figure was 57 per cent. He presents evidence, however, which seems to show that the results were determined by the grade of the tumor and the condition of the axillary lymph nodes rather than by the irradiation. He is unable to determine whether these conditions were influenced by the irradiation. He believes that 90 per cent five year survivals can be brought about by surgery alone in Grade I cases.

In a group of 20 cases treated by simple excision followed by irradiation there were 42 per cent five year survivals. A study of these tumors shows that many of them were low grade but there is also some evidence that the irradiation influenced the results.—*Audrey G. Morgan.*

Hill, Robert P., and Stout, Arthur Purdy. Sarcoma of the breast. *Arch. Surg.*, April, 1942, *44*, 723–759.

This is a discussion of the classification of sarcoma of the breast, a subject in which there has been a great deal of confusion. Many of the cases formerly classified as sarcoma have proved to be atypical forms of carcinoma or benign tumor. At present the incidence of sarcoma is reported as 0.5 to 3 per cent of all malignant breast tumors instead of the 6 to 9 per cent formerly reported.

Formerly mammary sarcoma was classified as adenosarcoma and pure sarcoma. The author

separates the latter into several types and gives a classification of (1) adenofibrosarcoma; (2) fibrosarcoma; (3) lymphoblastoma; (4) malignant hemangioendothelioma; (5) liposarcoma and myosarcoma, and (6) mixed tumor.

Photomicrographs of these different types of tumor are given and a table showing the outstanding features and results of treatment in 24 cases.

The most frequent form of sarcoma of the breast is adenofibrosarcoma, which is a sarcomatous transformation of fibroadenoma. It is generally benign clinically, but true fibrosarcoma which develops from the connective tissue of the breast is as malignant as similar tumors in other parts of the body.

If there is cartilage or bone in a breast tumor it does not necessarily show that it is a teratomatous mixed tumor. It is more apt to result from metaplasia in a fibrosarcoma or adenofibrosarcoma.

The other forms, myosarcoma, liposarcoma and malignant hemangioendothelioma and lymphoblastoma are unusual and particularly malignant forms which usually run a rapid course.

Other terms often used in the classification of sarcoma of the breast only add to the confusion which already exists on the subject.—*Audrey G. Morgan.*

MURPHY, JAMES B. Analysis of the trends in cancer research. *J. Am. M. Ass.*, Sept. 12, 1942, *120*, 107–111.

During the last four decades an impressive number of definite fundamental facts regarding the nature of malignancy has been established. Some three years ago a committee appointed by the Surgeon General of the Public Health Service made an attempt at a "formulation and clarification" of the mass of knowledge already accumulated from experimental studies. For this paper the author selected a few of the more important contributions which served as a basis for the conclusions arrived at in the report of this committee.

The fact that tumors can be transplanted in series demonstrates that malignancy is centered in the cells, since the new tumors which result from inoculation are formed entirely by the multiplication of the introduced cells. The intimate contact between the host's tissues and that of the tumor, for which it supplies blood vessels and supporting stroma, does not lead to a cancerization of the host cells.

The tendency to develop some types of malignancy is definitely inherited. The inherited tendency or predisposition to develop cancer is not a general character but is confined in the strains of animals studied to a definite organ or tissue type. Thus one family may have the tendency for lung tumors, another mammary cancer, and a third leukemia. There is some evidence that this predisposition for special types of cancer holds also for man. The results of foster nursing have given evidence of the presence of a factor in the milk which definitely modifies or augments the inherited tendency for breast cancer. Mice from a high cancer strain, fostered by a female from a low strain, have a definitely lower breast cancer rate than litter mates nursed by their own mothers. The reverse conditions, namely young from a low cancer strain fostered by females from a high strain, result in a higher mammary cancer rate in the fostered animals than in the controls.

Tumors may be experimentally induced by so-called carcinogenic agents. Among these are hydrocarbons, including dibenzanthracene, benzpyrene and methylcholanthrene, roentgen rays, radium, ultraviolet light, infectious agents and larger parasites. The carcinogenic agents have nothing in common among themselves except the effect they produce in the tissues. There is still no understanding of the mode of action of the carcinogenic agents.

New properties of cells may develop under the influence of carcinogens. The production of liver cancer by the azo dye butter yellow in animals on a deficient diet and the prevention of the carcinogenic effect by additions to the diet offers a chance to establish the mechanism in at least one instance. There is evidence that a breakdown product of the dye affects certain enzyme systems of the liver cells and that cancer cells resulting from this action show a certain amount of immunity to the toxin.

In selecting strains of animals for cancer experiments the importance of genetic constitution and predisposition has become more and more evident. Strains of animals inbred to a point where there is a high degree of genetic homogeneity are now considered almost essential. It is equally essential to have full information as to hereditary and predisposing factors for the various types of malignancy possessed by the animals utilized. A host of agents, chemical, physical and biologic, known as carcinogens may be the inciting factors leading up to

the malignant state but they may be considered as only starting a series of tissue events or conditions tending to progress into malignancy. It is probable that substantial advancement in the methods of treatment will come only with a fuller knowledge of the mechanism by which the growth capacity of the cancer is maintained. The author concludes that:

1. Malignancy is a universal cell potentiality in that any cell has inherent in its makeup the potentiality for unlimited or uncontrolled growth.

2. The dgree of this potentiality for malignancy is a variable quantity for each tissue or cell type, and this degree is determined largely, if not entirely, by hereditary or predisposing factors.

3. The malignancy potentiality of a cell may be developed in the more sensitive groups by the strain of normal physiologic processes but may be set off even in resistant groups by a variety of inciting agents.

4. The change from a normal to a malignant cell represents an alteration in the cell itself, by virtue of which proliferation becomes an automatic process independent of a continuously acting provocative agent.

5. The new property of the cell appears to develop suddenly, and this becomes a fixed character which is transmitted to all its descendants. It may possibly be the result of a somatic mutation.—*S. G. Henderson.*

Paul, Lester W., and Pohle, Ernst A. Radiation osteitis of the ribs. *Radiology*, May, 1942, *38*, 543–551.

The authors make routine roentgen examinations of the chest when their patients return for re-exmination after treatment for cancer of the breast. Among these patients they have found 15 in whom the ribs had been injured by the irradiation. They showed fracture and rarefaction and absorption of bone at the site of the fracture. In 4 of the cases the fractures healed after ten months, 1 was not followed up and in the other 10 there was no healing after three years. A table is given showing the dosage, length of treatment and clinical features of the cases. The fractures were all in the anterior part of the upper ribs where there is most apt to be overlapping of fields and where there is the greatest amount of scattered radiation from different fields. These fractures from roentgen injury must be differentiated from traumatic fracture and metastasis. There is no history of accident to account for traumatic fracture and when they are observed over a period of time there is no progress of the lesions as there would be in metastasis.

These pathological fractures are late reactions. In 10 of these cases a total dose of 5,200 to 6,600 r was given over periods of from thirteen to thirty-six months. The others were given smaller doses, the smallest being 3,200 r over a period of three months. There were no symptoms from these fractures and they were discovered by chance on routine chest examination. The fact that they occur need not prevent the giving of the necessary amount of radiation for treatment of the cancer.—*Audrey G. Morgan.*

Graves, R. C., and Lawrence, K. B. Bilateral embryonal carcinoma of the testicle, with a note on the technique of orchidectomy for malignant disease. *J. Urol.*, April, 1942, *47*, 482–490.

Approximately 50 cases of bilateral malignant disease of the testicles have been reported. In a series of 292 cases of teratoma testis at the Memorial Hospital no instance of bilateral involvement was noted. It is debatable whether these bilateral tumors arise independently of each other or whether one tumor represents metastasis from the other.

The authors report the case of a male, aged thirty-three, who had had a right testicular swelling for two and a half years and a left testicular swelling for eighteen months. A mass had been present in the abdomen for one month, apparently retroperitoneal. Hormonal tests of the urine revealed an F.S.H. assay of 80 mouse units per liter. Roentgenograms of the chest showed no evidence of metastasis.

A bilateral orchidectomy was performed. The histopathological diagnosis was embryonal carcinoma. Eight days postoperatively roentgen therapy was instituted. A total dosage of 1,200 r in air was given to each of the following eight fields; right and left anterior and posterior pelvis, and right and left anterior and posterior abdomen; 10×15 cm. fields were used on the abdomen and 10×10 cm. fields on the pelvis. The factors were 200 kv., 50 cm. distance, filter of 0.5 mm. copper and 1 mm. aluminum; 200 r was delivered per treatment.

Two weeks after completion of this cycle no abdominal mass could be palpated and no

lymphatic nodes. Ten months after operation there was no evidence of residual disease clinically.

The authors had previously given roentgen irradiation before operation in malignant tumors of the testicle but are now making exceptions in the case of a very early tumor where the diagnosis can only be suspected and in the case of the large bulky tumors. They advise a radical operative procedure with immediate postoperative irradiation in these cases.—*R. M. Harvey.*

Herger, C. C., and Sauer, H. R. Occurrence and clinical course of radium reactions following use of radon implants in treatment of carcinoma of the bladder. *J. Urol.*, Feb., 1942, *47*, 141–147.

There are immediate and late reactions to interstitial radon implantations. Immediate reactions include ulcerations at the implantation site. If these reactions persist they lead to infection, stone formation and symptoms of frequency and dysuria. Late effects are telangiectases which may rupture and cause severe hematuria and obstructive uropathies which follow ureteral strictures from scar formation. This type of obstruction may cause renal colic or lead to kidney death without symptoms.

The authors treated 279 bladder tumors with radon implantations in an eleven year period. The implants were 5 mm. in length and had a filter of 0.3 mm. of gold. They contained from 1.0 to 2.5 mc. of radon. Two hundred and twenty-nine patients of the total of 279 were available for this study. Of these 50 were treated by radon alone; 179 received roentgen irradiation, radium packs and electrocoagulation alone or in combination with the interstitial irradiation.

The authors obtained five year cures in 31.6 per cent of 114 cases treated from 1930 to 1935. The late reactions were few. Four cases developed unilateral ureteral strictures and 4 other cases had bleeding from telangiectases.

The early reactions were more common. Thirty-four cases had no evidence of radium reaction and more than two-thirds of this group are alive and well. Ninety-five cases had ulcers which healed without evidence of residual tumor and 60 per cent of this group are known to be alive and well. In 8 cases the ulcer healed but residual tumor persisted. In this group 2 cases are still alive with evidence of tumor.

Twenty-nine cases had persistent ulcers without evidence of tumor; 5 of these cases are alive and well. In 65 cases both ulcer and tumor persisted and only 4 of this group have survived.

The occurrence of ulceration and the tendency of ulcers to heal was directly dependent on the tumor type. Grade 1 carcinoma developed the least number of ulcers and showed greatest tendency to healing of ulcerations which did develop. Grade 3 carcinomas showed the greatest number of ulcers and the least tendency to healing.

Location of the tumor was of importance in the development and healing of ulcers. Tumors around the internal vesical orifice did not tolerate radon irradiation well. Also tumors in the center or border of the trigone showed little tendency to healing of ulcers which formed. The most favorable sites for treatment in regard to failure of ulceration to develop were on the anterior and posterior bladder walls.

The duration and ultimate fate of radium ulcerations were found to depend directly on the size of the area treated and the size of the ulceration which developed. No lesion smaller than 1.0 cm. in diameter developed an ulcer and all lesions larger than 5.0 cm. developed ulcers.

The duration and fate of ulcerations was also dependent directly on the amount of irradiation delivered to the tumor. Where more than 3,000 mc-hr. was delivered to the tumor two-thirds of the cases developed ulcers which persisted. Where less than 1,000 mc-hr. was delivered to the tumor only 16.7 per cent developed persistent ulcers. The incidence of persistent ulceration also depended directly on the number of separate implantations of radon. Finally those patients in whom stones and incrustations developed had a longer duration of radium ulcers. —*R. M. Harvey.*